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Dermatologic and Ophthalmic Drugs Advisory Committee Meeting Briefing Document

Title:	**Sodium Hyaluronate Ophthalmic Solution 0.18% for the Treatment of the Signs and Symptoms of Dry Eye Disease**
NDA Number:	**22-358**
Product Name:	**Sodium hyaluronate ophthalmic solution 0.18%**
Active Ingredient:	**Sodium hyaluronate**
Indication:	**For the treatment of the signs and symptoms of dry eye disease**
Sponsor:	**River Plate Biotechnology, Inc. 100 Europa Drive, Suite 421 Chapel Hill, NC 27517 919-960-0217**
Meeting Date:	**June 26, 2009**

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EXECUTIVE SUMMARY

Background

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort and visual disturbance, related to tear film instability with potential damage to the ocular surface (Lemp, 2007). It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. Any modifications of the lipid, aqueous, or mucus components of the tear film may affect the homeostasis of the ocular surface, leading to dry eye disease. In addition, inflammation of the surface of the eye may occur along with dry eye. If left untreated, this condition can lead to pain, ulcers, or scars on the cornea, and some loss of vision. However, permanent loss of vision from dry eye is uncommon.

Dry eye can be associated with immune system disorders such as Sjögren's syndrome, lupus, and rheumatoid arthritis. Sjögren's syndrome, a leading etiology of dry eye, is an autoimmune disorder in which immune cells attack and destroy the glands that produce tears and saliva and leads to inflammation and dryness of the mouth, eyes, and other mucous membranes.

In the United States (US), an estimated 3.23 million women and 1.68 million men, a total of 4.91 million people aged 50 years and older, are affected by dry eye disease (Tsubota, 1992; Craig, 1997). Dry eye symptoms are one of the most common reasons a patient will visit an ophthalmologist (Schaumberg, 2003). A rapid treatment effect realized by administration of a topical agent that mimics the natural tears would be advantageous in the treatment of this disease, given its propensity to irritate and damage subjects' eyes, affect vision, and decrease quality of life.

Natural tears have variable viscoelastic behavior; they are viscous under static conditions in the eye, while they are much less viscous during blinking. The sodium salt of hyaluronic acid, sodium hyaluronate (SH), is the active ingredient in this proprietary formulation of SH ophthalmic solution 0.18%, which is being reviewed by the Food and Drug Administration (FDA) as a prescription product for the treatment of dry eye disease. Sodium hyaluronate was chosen early in the development as the active ingredient in the drug product because of its viscoelastic properties, which allow it to behave differently during and between blinks (Bron, 1985; Tiffany, 1994). During blinks, shear stress causes the molecules of SH to align with each other. As a result, the solution becomes elastic and relatively nonviscous and spreads easily over the surface of the cornea. Between blinks, the molecules of SH form a tangled meshwork, and the solution becomes less elastic and more viscous. This stabilizes the precorneal tear film and maximizes the residence time of the solution on the surface, enabling it to lubricate and protect the ocular surface. Additionally, SH exhibits

water entrapping and mucoadhesive properties, which delays evaporation from the eye surface.

Goals for treatment of patients with dry eye disease are improvement of ocular comfort and quality of life, and a return of the ocular surface and tear film to a normal homeostatic state. For approval of a new prescription drug for the treatment of dry eye disease, the FDA requires demonstration of efficacy for both a sign (objective) and a symptom (subjective) of the disease. This requirement has historically been a challenge for new products and no products have yet been approved by the FDA for the treatment of the signs and symptoms of dry eye disease. Restasis is labeled as a treatment to increase tear production in patients that have suppressed tear production caused by inflammation.

Current therapies for the management of some of the symptoms of dry eye disease include tear supplementation (artificial tears), retention and stimulation, anti-inflammatory agents, and environmental strategies (Dry Eye Work Shop, 2007). For example, secretagogues, which focus on stimulating the secretion of tears and glycoproteins, as well as lubricants, which lubricate the surface of the eye, appeared to be effective in early studies. Two of these, Prolacria™ (diquafosol tetrasodium, Inspire), which targets the P2Y2 receptor, and rebamipide (Novartis), which stimulates mucin secretion, have not emerged successfully from Phase 3 development. Prolacria™ is being tested in a fifth Phase 3 study, after the reporting of placebo effects similar to the active, lack of reproducibility in the endpoints, and meeting the objective but not the subjective endpoint in previous Phase 3 studies. The most recent of the Phase 3 studies of rebamipide has been completed for more than 2 years; however, a New Drug Application (NDA) has not yet been reported as having been filed. It is possible that the study results did not achieve both an objective and a subjective endpoint and/or that the development of the product has been abandoned.

Other late-stage clinical compounds appear to have experienced developmental and/or regulatory setbacks in the last 3 years. For example, Allergan's Androgen Tears® was reported to be in Phase 2/3 trials; however, no development has been reported on this product in the last 3 years. It is possible that the product may have been abandoned as a drug candidate.

Hyaluronic acid occurs naturally in all vertebrates in the vitreous body of the eye, extra-cellular matrix of the skin, and synovial fluid. It is a biopolymer of disaccharide units composed of N-acetylglucosamine and glucuronic acid in linear chains of varying molecular weights. Sodium hyaluronate is currently used as an active ingredient in other medicinal products and medical devices (Appendix 10.1), especially in ocular surgery involving the anterior or posterior segment of the eye where it is used to maintain the shape of the structure, to cover surgical instruments, and to protect the sensitive corneal endothelium from

further surgical damage. In the US, sodium hyaluronate is listed as an inactive ingredient in an over-the-counter (OTC) product (Blink® Tears) intended to lubricate the eyes. The formulation, SH ophthalmic solution 0.18%, has been marketed in Europe, Australia, and parts of Asia since January 1998 under the trade names Vismed®, Vislube®, and Hylovis®. It has been approved as a Class IIb medical device in 41 countries and as a drug in 2 countries. Approximately 9.5 million product units were sold during the period between launch in January 1998 and December 31, 2008. The Sponsor continued clinical development of SH ophthalmic solution 0.18%, previously conducted in Europe, for the treatment of both the signs and symptoms of dry eye disease in the US. The US development initiatives, additional European studies, and studies published in the literature are the subject of the NDA 22-358.

A clinical program of 10 studies was conducted, including open-label studies, randomized studies comparing SH ophthalmic solution 0.18% with artificial tears, and two randomized, double-blind, well-controlled studies, which compared SH ophthalmic solution 0.18% with vehicle placebo or saline placebo. To meet the regulatory requirement for approval, the objective endpoint evaluated in the analysis of the two studies for SH ophthalmic solution 0.18% was the change in lissamine green staining scores and the subjective endpoint was the change in symptom frequency scores.

Vital dyes, particularly lissamine green, stain exposed epithelial cells that have been deprived of mucin protein protection. The dye is utilized for its ability to test for conjunctival surface and corneal integrity and to determine where the tear film is discontinuous. The primary subjective endpoint, global symptom frequency score, is a composite score. In both studies, subjects rated the frequency of 5 individual symptoms (burning, scratchiness, grittiness, dryness, and soreness) as a single value on both eyes together (0 = never, 1 = sometimes, 2 = often, 3 = constantly). The global score is the sum of the 5 individual scores.

Efficacy Results

The first randomized, placebo-controlled Phase 3 clinical study conducted with the proprietary formulation of SH ophthalmic solution 0.18% described herein versus saline placebo (Baudouin 2005), demonstrated benefit on both an objective sign (lissamine green staining) and a subjective symptom (global symptom frequency) at 7 and 28 days. Although these endpoints were secondary, their results were robust.

These same endpoints of efficacy were used in Study RP-001, a randomized, vehicle placebo-controlled study conducted with FDA approval under a Special Protocol Assessment (SPA) review. The benefits in the reversal of erosion of the cornea and conjunctiva, assessed by lissamine green staining, and relief from symptoms, assessed by global symptom frequency, with SH ophthalmic solution 0.18% were apparent after 1 week of treatment in

Study RP-001, a time point that was selected to assure the replication of the Baudouin 2005 study results. For most objective and subjective outcomes assessed, SH ophthalmic solution 0.18% was more effective than the saline placebo in the Baudouin 2005 study and more effective than the vehicle placebo in Study RP-001 in relieving the signs and symptoms of dry eye. Results from the Baudouin 2005 study showed that SH ophthalmic solution 0.18% was more effective than the saline placebo in reducing the following objective and subjective measures of dry eye: corneal fluorescein staining at Day 28, lissamine green staining at Days 7 and 28, and global symptom frequency at Days 7 and 28. Results from Study RP-001 showed a statistically significant result for SH ophthalmic solution 0.18% over the vehicle placebo in improving lissamine green staining scores at Day 7 (primary objective endpoint) and a supportive trend at Day 14. The difference from baseline in global symptom frequency scores at Day 7 was statistically significant (primary subjective endpoint) and a supporting trend was observed in summed visual analogue scale (VAS) symptom scores, and composite symptom intensity and symptom frequency scores at Day 7.

These data collectively demonstrate the desirable feature of reproducible efficacy observed as early as 7 days. By comparison, the reported onset of action for Restasis® is 2 months or more. Restasis® is not approved for the treatment of the signs and symptoms of dry eye disease; rather, it is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with dry eye disease. However, it is the only prescription product routinely prescribed by physicians as an adjunct to the treatment of dry eye. If approved, SH ophthalmic solution 0.18% will be the first product indicated for the treatment of the signs and symptoms of dry eye disease. It features the added benefit of providing patient relief from both the signs and symptoms of the disease within 7 days.

In addition to two pivotal Phase 3 studies, worldwide post-marketing clinical experience data, data from published nonclinical safety studies, and data from the clinical development have been described to provide a comprehensive assessment of the safety and efficacy of SH ophthalmic solution 0.18% for the treatment of the signs and symptoms of dry eye disease. Studies supportive of the efficacy of SH ophthalmic solution 0.18% demonstrated the efficacy of SH ophthalmic solution 0.18% in additional recognized endpoints. For example, the unique ability to increase the number of goblet cells, which stimulate mucus production, and decrease tear osmolarity to normal physiological levels, or the increase in tear film break-up time (TBUT) values for up to 4 hours after instillation.

To support the marketing application, 8 other clinical studies assessed the efficacy of this proprietary formulation of SH ophthalmic solution 0.18% in 512 subjects who were treated with study drug for up to 2 months. Five of these studies were randomized and controlled and three were uncontrolled and exploratory. The results from individual studies of SH

ophthalmic solution 0.18% compared with a placebo or active control showed statistically significant differences on the integrity of the cornea and conjunctiva, as measured by lissamine green staining; tear production, as measured by Schirmer's I test; integrity of the tear film, as measured by TBUT; and content of cells of the surface conjunctival epithelium, as measured by impression cytology.

Safety Results

Clinical studies and post-marketing reports demonstrate that SH ophthalmic solution 0.18% is well tolerated for the treatment of the signs and symptoms of dry eye disease.
Three randomized and controlled studies conducted with SH ophthalmic solution 0.18% form the basis of the safety profile reflected in the proposed labeling: one Phase 2 study (Baudouin 2001) and two Phase 3 studies (Baudouin 2005 and Study RP-001). The results of these studies show that the safety profile of SH ophthalmic solution 0.18% is excellent, with a very low incidence of adverse events (AEs). Of the 305 subjects who received the active treatment in the three studies, 67 experienced 1 or more AEs (1 AE reported, n = 44; > 1 AE reported, n = 23) and only 1 subject experienced a serious adverse event (SAE), which was considered to be unrelated to SH ophthalmic solution 0.18%. Across the three studies, 3 subjects treated with the product withdrew due to AEs, all of which were judged to be unrelated or possibly related to product. Because the product is an ophthalmic solution delivered by topical instillation, ocular AEs are of greatest clinical relevance. Across studies, the ocular AEs were predominantly mild and few were judged to be related to the product.

From the launch of this proprietary formulation of SH ophthalmic solution 0.18% in other parts of the world, in January 1998 until the 1st quarter of 2008, only 39 reports of medical complaints were filed through spontaneous product surveillance reporting systems. All events reported were rated mild to moderate in intensity. None of the reported events required changes to the product safety labeling.

Overall, the clinical safety data for SH ophthalmic solution 0.18% presented in this summary show that the product is safe and well tolerated. During more than 10 years of research and marketing activities, very few AEs have been documented in either clinical studies or post-marketing reports of the product. Based on this evidence and the favorable results from the nonclinical studies, SH ophthalmic solution 0.18% has an excellent safety profile.

Conclusions

The safety of SH is widely established in the studies contained herein and elsewhere, and the benefit-to-risk evaluation is overwhelmingly positive. Ten studies have assessed the efficacy of SH ophthalmic solution 0.18% in 512 subjects who were treated with the product for up to 2 months. Seven studies were randomized and controlled and three were uncontrolled and

exploratory. The results from individual studies showed statistically significant benefits of the product when compared with a placebo or active control.

The results of two randomized, controlled Phase 3 clinical studies conducted with the product show significant benefit in both an objective sign (lissamine green staining) and a subjective symptom (global symptom frequency). This finding is notable because investigators in numerous clinical studies with other products have been unable to achieve significant differences over control in both an objective sign and a subjective symptom in subjects with dry eye disease. The FDA requirement to demonstrate efficacy in both a sign and a symptom using the product's vehicle as a control has proven to be a significant hurdle for other candidates in development for the treatment of the signs and symptoms of dry eye disease. The efficacy of SH ophthalmic solution 0.18% using the vehicle of the formulation as a control was demonstrated by Study RP-001. Thus, the superiority of this formulation of SH ophthalmic solution 0.18% has been demonstrated in the same sign and the same symptom when compared with a saline placebo in the Baudouin 2005 study and compared with a vehicle placebo in Study RP-001, with an early onset of action observed at 7 days. This is compelling and scientifically thorough evidence of the efficacy of the product in patients with dry eye disease.

Data from the post-marketing clinical experience, data from published nonclinical safety studies, and data from the clinical development program have been integrated to provide an assessment of the comprehensive safety and risk assessment of SH ophthalmic solution 0.18% for the treatment of the signs and symptoms of dry eye disease. The findings are supportive of a favorable risk-benefit profile for regulatory approvability of this formulation of SH ophthalmic solution 0.18% in the treatment of the signs and symptoms of dry eye disease.

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LIST OF ABBREVIATIONS

Abbreviation	Definition/Term
ADME	Absorption, distribution, metabolism, and elimination
AE	Adverse event
ANCOVA	Analysis of covariance
BCVA	Best corrected visual acuity
BSS	Buffered saline solution
CAE	Controlled Adverse Environment
CD44	Cluster of differentiation 44; Hyaluronic acid receptor
CD63	Cluster of differentiation 63; LAMP-3 lysosomal-membrane-associated glycoprotein
CLV	Carboxymethylcellulose
CRF	Case Report Form
eCRF	Electronic Case Report Form
F	Female
FDA	Food and Drug Administration
FKA	Formerly known as
HLA-DR	Human leukocyte antigen DR; Class II major histocompatibility complex antigen
HPMC	Hydroxypropylmethylcellulose
IB	Investigator's Brochure
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent to treat
KCS	Keratoconjunctivitis sicca
LOCF	Last observation carried forward
M	Male
MedDRA	Medical Dictionary of Regulatory Activities
mm	Millimeter
mmHg	Millimeters of mercury
MUC5AC	Mucin protein secreted by goblet cells
NA	Not applicable

Abbreviation	Definition/Term
NDA	New Drug Application
NIBUT	Noninvasive break-up time
NSAIDs	Non-steroidal anti-inflammatory drugs
OCI	Ocular comfort index
OTC	Over-the-counter
PP	Per protocol
SAE	Serious adverse event
SD	Standard deviation
SPA	Special Protocol Assessment
SH	Sodium hyaluronate
TBUT	Tear film break-up time
TEAE	Treatment-emergent adverse event
UIC2	P glycoprotein
US	United States
VAS	Visual analogue scale

1. Background and Scientific Rationale

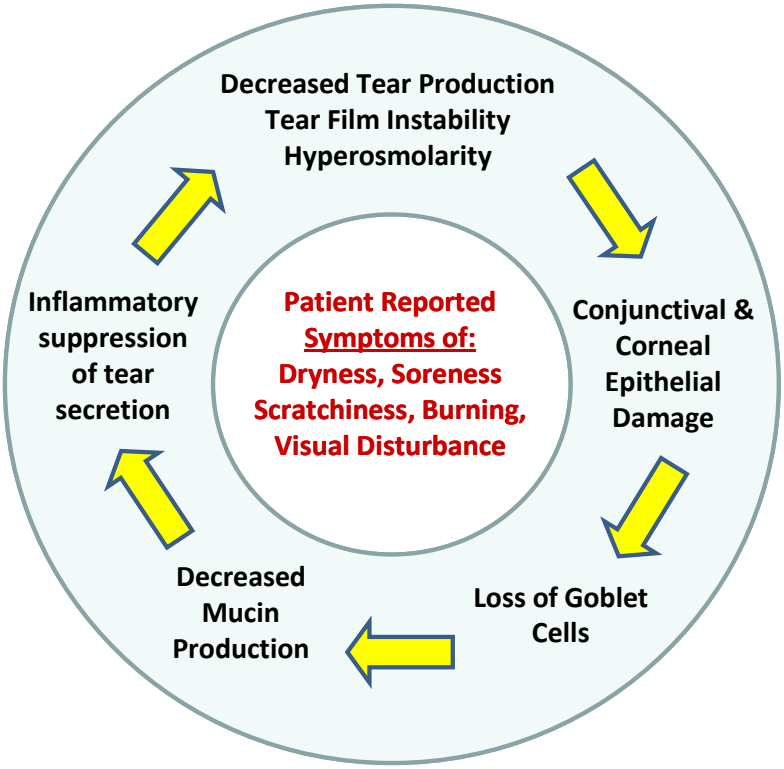
1.1 Overview of Dry Eye Disease and Current Practice for Treatment

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort and visual disturbance, related to tear film instability with potential damage to the ocular surface (Lemp, 2007). It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. Any modifications of the lipid, aqueous, or mucus components of the tear film may affect the homeostasis of the ocular surface, leading to dry eye disease.

Dry eye disease affects a significant percentage of the population. In the United States (US), an estimated 3.23 million women and 1.68 million men, a total of 4.91 million people aged 50 years and older, are affected by dry eye disease (Tsubota, 1992; Craig, 1997). Dry eye symptoms are one of the most common reasons a patient will visit an ophthalmologist (Schaumberg, 2003). Patients with dry eye disease (diagnosed as keratoconjunctivitis sicca; KCS) experience dry-, gritty-, or scratchy-feeling eyes, burning or itching in the eyes, redness, blurred vision, or a sensation of a foreign body in the eye. Symptoms often worsen in dry climates, in windy conditions, with higher temperatures, with lower humidity, and with prolonged use of the eyes (eg, reading, using a computer, or watching television). The prevalence of dry eye disease is particularly high in patients with autoimmune disease (especially Sjögren's syndrome), elderly patients, and postmenopausal women (Schaumberg, 2003).

The primary causative mechanisms of dry eye are tear hyperosmolarity and tear film instability. Tear hyperosmolarity can cause damage to the surface of the epithelium. The epithelial damage involves cell death, particularly the loss of goblet cells, responsible for secreting mucins onto the ocular surface. The damage to the ocular surface and disruption of mucin production leads to tear film instability. The instability exacerbates the ocular surface hyperosmolarity. This ongoing cycle of dryness and irritation eventually leads to corneal erosion. The erosion exposes nerves, translating into pain (Figure 1).

Figure 1 Cascade of Events Leading to Dry Eye



Goals for treatment of patients with dry eye disease are improvement of ocular comfort and quality of life, and a return of the ocular surface and tear film to a normal homeostatic state. Current therapies for the management of dry eye disease include tear supplementation, retention and stimulation, anti-inflammatory agents, and environmental strategies (Dry Eye Work Shop, 2007). However, there are currently no prescription products approved by the Food and Drug Administration (FDA) for the indication of the treatment of the signs and symptoms of dry eye disease.

For approval of a new prescription drug, such as sodium hyaluronate (SH) ophthalmic solution 0.18%, for the treatment of dry eye disease, the FDA requires demonstration of efficacy for both a sign (objective) and a symptom (subjective) of the disease. This criterion has historically been a challenge for new products, and although several new drug candidates have undergone clinical testing in the US for the treatment of dry eye disease, none have yet been approved for this indication. For example, secretagogues, which focus on stimulating the secretion of tears and glycoproteins, as well as lubricants, which lubricate the surface of the eye, appeared to be effective in early trials. However, Prolacria™ or diquafosol tetrasodium (Inspire) which targets the P2Y2 receptor and rebamipide (Novartis) which stimulates mucin secretion, have been delayed in development and are still in Phase 3 development. Inspire reported its first Phase 3 study results with Prolacria™ for the treatment

of dry eye in 2002. There was improvement in corneal staining with Prolacria™, however a similar improvement was observed with placebo. In the second Phase 3 study, corneal staining was statistically significant over placebo at 6 weeks (primary objective endpoint). The primary subjective endpoint for the study, clearing of the ocular symptom of foreign-body sensation at 6 weeks, did not meet statistical significance.

A third Phase 3 study was conducted and included assessments from both a conventional environmental component and an experimental Controlled Adverse Environment (CAE) chamber designed to exacerbate dry eye. In the environmental portion of the study, treatment with Prolacria™ resulted in statistically significant improvements in ocular staining (objective endpoint) compared to placebo. In the experimental CAE chamber portion of the study, statistical significance was not achieved with respect to the primary endpoints of ocular staining and discomfort (subjective endpoint) after exposure in the CAE chamber.

A fourth Phase 3 study failed to demonstrate statistically significant improvement as compared to placebo for the primary endpoint of the incidence of corneal clearing. An amendment to the NDA was submitted by Inspire in June 2005, and an additional approvable letter was received in December 2005. In January 2009, Inspire initiated a Phase 3 study for Prolacria™ under a Special Protocol Assessment (SPA) agreement with the FDA.
Three other late-stage clinical compounds appear to have experienced developmental and/or regulatory setbacks in the last 3 years. Rebamipide (Novartis) was reported to have completed a second Phase 3 study more than 2 years ago; yet no discernible progress has been made since that time. Public sources do not disclose the filing of an NDA, nor interaction with the Agency regarding the status of the development. It is possible that the study results did not achieve the desired endpoints and/or that the development of the product has been abandoned. Additionally, Allergan's Androgen Tears® was reported to be in Phase 2/3 studies; however, no development has been reported on this product in the last 3 years. It is possible that the product may have been abandoned as a drug candidate.

A principal problem encountered in clinical studies of drug candidates for dry eye disease is the observation that subjects receiving placebo drops (either saline or vehicle) often demonstrate improvement. Possible reasons for this include greater compliance in subjects participating in clinical studies, the general lubrication effects of the vehicle for many eye drops, and a regression to the mean in subjects recruited on the basis of findings that may be variable over time (Lemp, 2008; Foulks, 2003).

The requirement of efficacy for both a sign (objective) and a symptom (subjective) of the disease has been challenging to demonstrate. A reason for this may lie in the fact that the cascade of events leading to deterioration of the cornea can often lead to reduced corneal sensitivity ([Figure 1], Schein, 1997; Xu, 1996). This reduced sensitivity can further

confound the study of dry eye therapies; correction of ocular surface damage by an effective treatment could actually lead to more symptoms reporting in the short term due to the reemergence of corneal sensitivity.

1.2 Rationale for Development of Sodium Hyaluronate Ophthalmic Solution 0.18%

The active ingredient in SH ophthalmic solution 0.18% is the sodium salt of hyaluronic acid, sodium hyaluronate. Hyaluronic acid is a naturally occurring biological substance that is ubiquitous in mammalian connective tissues, including vitreous body and synovial joints. Since the product is presented as a sterile solution, there is no need to include a preservative. Preservatives have been associated with ocular irritation (Noecker, 2001; Asbell, 2006).

Sodium hyaluronate was chosen as the active ingredient in the drug product because of its unique viscoelastic properties, which allow it to behave differently during and between blinks (Bron, 1985; Tiffany, 1994). During blinks, shear stress causes the molecules of SH to align with each other. As a result, the solution becomes elastic and relatively nonviscous and spreads easily over the surface of the cornea. Between blinks, the molecules of SH form a tangled meshwork, and the solution becomes less elastic and more viscous. This stabilizes the precorneal tear film and maximizes the residence time of the solution on the surface, enabling it to lubricate and protect the ocular surface. Additionally, SH exhibits water entrapping and mucoadhesive properties, which delay its evaporation from the eye surface.

The active ingredient in SH ophthalmic solution 0.18% is obtained by bacterial fermentation from strains of *Streptococcus equi*, including *Streptococcus zooepidemicus,* and is a specific fraction with a high degree of purity and a restricted molecular weight range. Other marketed products containing SH use a form derived from cocks comb. The purification techniques used for SH derived from avian tissues yields a product that cannot be administered to patients with known allergies to avian proteins, feathers, and/or egg products. Sodium hyaluronate purified from bacterial fermentation does not show appreciable toxicity or immunosensitizing activity.

The vehicle of SH ophthalmic solution 0.18% is a balanced carrier, formulated to contain ions naturally present in the tear fluid to maintain the physiology of the cornea and, as such, closely resembles the natural tear film. The product has also been formulated to be hypotonic to compensate for the hypertonicity of natural tear film in subjects with dry eye disease.

SH ophthalmic solution 0.18% has been marketed in Europe, Australia, and parts of Asia since January 1998, under the trade names Vismed®, Vislube®, and Hylovis®. It is approved as a Class IIb medical device in 41 countries and as a drug in 2 countries. In some countries, the product is sold as a contact lens lubricant, also with a Class IIb medical device

designation. Approximately 9.5 million product units were sold during the period between launch in January 1998 and December 31, 2008. It is estimated that approximately 2.8 million patients used the product during this period, and only 39 spontaneous post-marketing reports of medical complaints related to the product were received. None of the reported complaints required changes to the product safety labeling.

More than 20 products containing SH are currently marketed in the US (Appendix 10.1). Among these, an over-the-counter (OTC) product (Blink® Tears), intended to lubricate the eyes, cites SH as an inactive ingredient. These SH-containing products are used across multiple therapeutic areas via multiple routes of administration and have demonstrated favorable safety profiles in a variety of patient populations.

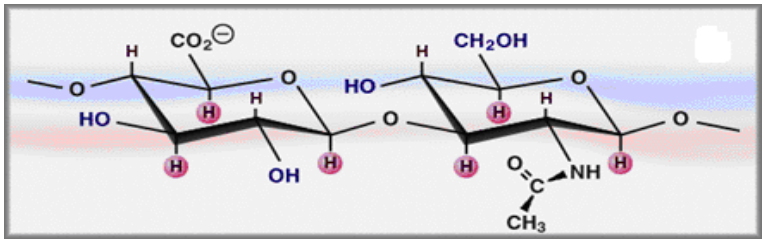
1.3 Description of the Product

1.3.1 Chemical Name and Structure

The active ingredient in the drug product is sodium hyaluronate, a biological polymer and member of the class of amino-sugar-containing polysaccharides known as the glycosaminoglycans.

The molecular formula for the product is $(C_{14}H_{20}O_{11}N_1Na_1)_n$, and the chemical structure is shown in Figure 2.

Figure 2 Chemical Structure of Sodium Hyaluronate



1.3.2 Formulation

The patented formulation of SH ophthalmic solution 0.18% contains the following:

Active ingredient: sodium hyaluronate 1.8 mg/mL

Inactive ingredients: calcium chloride, dibasic sodium phosphate, magnesium chloride, potassium chloride, sodium chloride, sodium hydroxide, sodium citrate, water for injection, and hydrochloric acid to adjust pH

1.3.3 Proposed Indication

Sodium hyaluronate ophthalmic solution 0.18% is indicated for the treatment of the signs and symptoms of dry eye disease.

1.3.4 Dosage and Administration

The dosing regimen used in the two Phase 3 studies (Baudouin 2005 and RP-001) ranged from 3 to 12 drops instilled into each eye per day. Subjects in the Baudouin study were instructed to instill 1 drop into both eyes at least 3 and up to 8 times per day as needed, while subjects in Study RP-001 were instructed to instill 1 to 2 drops into both eyes at least 3 and up to 6 times per day as needed. In the Baudouin 2005 study, subjects self-administered approximately 4 instillations daily as demonstrated by dosing diaries and calculation of study medication used relative to returned empty vials and unused study drug. In Study RP-001, subjects also self-administered approximately 4 instillations daily as demonstrated by calculation of study medication used relative to returned empty vials and unused study drug.

1.3.4.1 Dose rationale

Nonclinical studies established that SH ophthalmic solution 0.18% was safe at a daily exposure of up to 36 drops. In a 28-day nonclinical study in rabbits, quantities mimicking both the recommended human dose and a potential overdose were administered. Twenty rabbits received either 1 drop of SH ophthalmic solution 0.18% 6 times per day at hourly intervals (6 drops daily) or 3 drops of SH ophthalmic solution 0.18% 12 times per day at 30-minute intervals (36 drops daily). No findings of ocular intolerance related to SH ophthalmic solution 0.18% in either group were reported.

The effects of SH in solution concentrations ranging from 0% (vehicle only) to 0.3% on the prolongation of tear film break-up time (TBUT, see Section 4.3) were investigated in three clinical dose-finding studies (Hamano, 1993; Hamano, 1996; Sand, 1989). Investigators concluded that to be effective, the solution should have a minimum concentration of 0.1% SH, but a concentration of 0.2% SH was more effective (as measured by corneal staining and TBUT) and better tolerated than SH 0.1% or saline alone. Dosage formulation development work demonstrated that the optimum concentration for stability of the solution is 0.18%; therefore, the dosage formulation developed for evaluation in Phase 2 and 3 clinical studies was of this concentration. Phase 3 clinical studies demonstrated efficacy using the 0.18% formulation of SH ophthalmic solution. Therefore, this 0.18% concentration of SH solution is the dosage formulation proposed for approval.

In multiple clinical studies, treatment with SH ophthalmic solution 0.18% lead to a prolongation of TBUT. Compared with control treatment (hydroxypropylmethylcellulose, HPMC), Rolando (1994) and Rapisarda (1994) both reported significant increases in

TBUT in favor of SH ophthalmic solution 0.18% (both $P = 0.001$). In the Baudouin 2005 study, a trend for increased TBUT from baseline was observed. Two open-label, uncontrolled, short-term studies were conducted with SH ophthalmic solution 0.18%; Rimmer, et al (2000) showed a beneficial short-term effect of SH ophthalmic solution 0.18% on TBUT, as well as subjective symptoms. In that study, a 4-hour increase in TBUT (significant at 5, 15, and 30 minutes; $P < 0.05$), together with a reduction in dryness symptoms, was observed following the instillation of 1 drop of SH ophthalmic solution 0.18%. In a second short-term study, Montés-Micó, et al (2004) found that a single instillation of SH ophthalmic solution 0.18% improved optical aberrations, TBUT, and dry eye signs and symptoms. These results indicate that a single instillation of SH ophthalmic solution 0.18% was effective in stabilizing the tear film, decreasing the clinical symptoms, and increasing the comfort of subjects with dry eye symptoms.

The finding of an increase in TBUT lasting 4 hours (Hamano, 1993; Hamano, 1996; Sand, 1989) correlates well with clinical experience from the two Phase 3 studies in which subjects self-medicated on average 4 times per waking day, and support the dosing recommendation of 4-hour administration. This administration frequency is also supported by nonclinical data described in the following section.

SH ophthalmic solution 0.18%, indicated for treatment of the signs and symptoms of dry eye, will be prescribed under the care of a physician. The diagnosis of dry eye requires diagnostic testing for the signs and symptoms; the evaluation of corneal damage (ie, staining with vital dyes) is performed in a clinical setting.

2. Nonclinical Evaluation

No nonclinical toxicology, pharmacokinetic, and pharmacology studies were conducted by River Plate Biotechnology, Inc. for inclusion in the NDA 22-358. Published nonclinical data and human evidence of safety were provided in lieu of results from certain studies that would constitute a traditional nonclinical program. Upon review of published nonclinical study results and the excellent safety record that has been tracked since January 1998, the FDA indicated in the minutes of an August 2, 2006, Pre-Phase 3 meeting with the Sponsor that there were no apparent deficiencies in the nonclinical package (see Section 3.3). Therefore, the nonclinical pharmacology and toxicology data summarized in the NDA were obtained from the literature and by studies conducted at The Centre of Ocular Pharmacology, Faculty of Medicine and Surgery at the University of Studies, Catania, Italy or Research Toxicology Centre S.p.A., Rome, Italy and sponsored by Chemedica SA, Switzerland in support of the ocular administration of SH ophthalmic solution 0.18%.

2.1 Summary of Key Nonclinical Findings

The results of nonclinical toxicity studies with SH ophthalmic solution 0.18%, SL-1010 (SH obtained by bacterial fermentation), and SH purified from cocks combs (Denlinger, 1980a; Denlinger, 1980b; Nakagawa, 1984a; Nakagawa, 1984b) showed:

- Extrapolation of the nonclinical dose in a repeated-dose toxicity study in rabbits (ocular administration of bacteria-derived SH ophthalmic solution 0.18%; up to 36 drops per day for 28 days) to the dose used in clinical studies demonstrates a 3-fold margin of safety based on local exposure and a 50-fold margin of safety based on systemic exposure (assuming 100% absorption and a proposed clinical dosing regimen of 4 instillations of 1 to 2 drops into both eyes per day) (Study RTC 5427).
- No toxic effect following acute and subacute topical ocular administration of bacteria-derived SH ophthalmic solution 0.18% in albino rabbits and rabbits with pigmented eyes (Study SVS 20 12-93-01; Study SVS 12-93-02; Study RTC 5427).
- No cytotoxic effect on human conjunctival cells in vitro upon exposure to bacteria-derived SH ophthalmic solution 0.18% (Debbasch, 2002; Debbasch, 2000).
- No acute toxic effects following injection into the anterior chamber or vitreous body of monkey eyes with cocks comb-derived SH (Denlinger, 1980a; Denlinger, 1980b; Sawa, 1993).
- No acute toxic effects in rats or mice following oral, intraperitoneal, or subcutaneous administration of bacteria-derived SH (Morita, 1991a; Morita, 1991b; Wakisaka, 1991).
- No chronic toxic effects in rats or dogs following subcutaneous administration of bacteria-derived SH, with the exception of tissue hardening and/or edema at the injection site (which was reversible). All organs appeared normal at termination and no tumor formations were detected in either animal species (Morita, 1991b; Morita, 1991c; Nozaki, 1993).
- No fetal toxicity or teratogenic effects on the fetuses of treated dams with bacteria-derived SH (rats or rabbits) (Ohta, 1991; Tanaka, 1991a; Tanaka, 1991b; Wada, 1991).
- No detectable antigenicity in guinea pigs, mice, or rabbits after parenteral administration of cocks comb-derived SH (Nakagawa, 1984a; Nakagawa, 1984b).

No long-term carcinogenicity studies with SH were conducted in animals because hyaluronic acid is a naturally occurring biological substance that is ubiquitous in mammalian connective tissues, including vitreous body and synovial joints. In addition, there were no indications of possible carcinogenic effects of SH produced by fermentation during subacute and chronic toxicity testing in rats that received daily subcutaneous administration for up to 6 months, the results of in vitro and in vivo mutagenicity tests were negative, and there was a lack of absorption from the topical ocular route.

No nonclinical pharmacokinetic studies were conducted with SH ophthalmic solution 0.18%, although SH has been investigated extensively. Sodium hyaluronate is rapidly removed from the bloodstream, and it is quickly and efficiently degraded in the liver. There have been no clinical findings in human studies to indicate systemic adverse events (AEs) as evaluated by laboratory assessments. These findings lead to the conclusion that little or no systemic absorption of SH ophthalmic solution 0.18% occurs when instilled topically on the ocular surface. Any systemic circulation is unlikely to be of clinical consequence owing to the lack of clinical presentation of events and the very low concentration of SH in the ophthalmic solution.

These data indicate that the human exposure risk for systemic toxicity or teratogenicity after topical administration of SH ophthalmic solution 0.18% is very low. Furthermore, since the approval of the product in Europe, Australia, and parts of Asia in January 1998, no reports of carcinogenicity, mutagenicity, or teratogenicity have been associated with use of the product.

3. Clinical Development Program and Regulatory History

3.1 Overview

To date, 10 clinical efficacy and safety studies have been conducted with SH ophthalmic solution 0.18%, in which 512 subjects have been treated for periods ranging from a single instillation to repeated instillations daily for up to 2 months: Study RP-001 (1), Baudouin, 2005 (2); Rapisarda, 1994 (3); Rolando, 1994 (4); Baudouin, 2001 (5); Johnson, 2008 (6); Rimmer, 2000 (7); Montés-Micó, 2004 (8); Patel, 2001 (9); and Prabhasawat, 2007 (10). An overview of these 10 clinical studies is provided in Table 1.

Table 1 Clinical Studies with Sodium Hyaluronate Ophthalmic Solution 0.18% (SVS20, Vismed®)

Type of Study	Study Identifier; Study Period	Objective(s) of the Study	Study Design and Type of Control	Treatment(s); Dosage Regimen; Route of Administration	No. of Subjects (M/F)	Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report
Safety and Efficacy	RP-001 River Plate Biotechnology (2008) (**1**)	To compare the safety and efficacy of SH ophthalmic solution 0.18% to vehicle in subjects with dry eye disease	Phase 3, multicenter, randomized, controlled, double-masked	SH ophthalmic solution 0.18% and vehicle eye drops; 1-2 drops of either product in both eyes at least 3 and up to 6 times per day as needed Ocular instillation	N=444 SH 0.18% n=221 (49/172) Vehicle: n=223 (62/161)	Subjects with at least 3 months documented history of dry eye in both eyes diagnosed as dry eye disease, KCS, or due to Sjögren's syndrome	14 days	Completed; Full report
Safety and Efficacy	SVS20-99-04 Baudouin, 2005 (**2**)	To evaluate the safety and efficacy of SH ophthalmic solution 0.18% vs. saline solution in subjects with bilateral moderate dry eye disease	Phase 3, multicenter, randomized, controlled, double-masked, parallel-group	SH ophthalmic solution 0.18% and saline eye drops; 1 drop of either product into each eye at least 3 and up to 8 times per day as needed Ocular instillation	N=151 (126/25) SH 0.18% n=74 (61/13) Saline: n=77 (65/12)	Subjects with bilateral moderate dry eye disease or moderate dry eye disease due to Sjögren's syndrome	28 days	Completed; Full report

Abbreviations: F = Female; KCS = Keratoconjunctivitis sicca; M = Male; SH = Sodium hyaluronate.

Continued

Table 1 (cont'd) Clinical Studies with Sodium Hyaluronate Ophthalmic Solution 0.18% (SVS20, Vismed®)

Type of Study	Study Identifier; Study Period	Objective(s) of the Study	Study Design and Type of Control	Treatment(s); Dosage Regimen; Route of Administration	No. of Subjects (M/F)	Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report
Safety and Efficacy	Rapisarda, 1994 (**3**)	To compare the effect of SH ophthalmic solution 0.18% and HPMC/Dextran 70 (Dacriosol®) eye drops on tear volume and tear stability; to evaluate their effect on the osmolarity of the tear film; and to assess the tolerability of the 2 formulations	Phase 2, randomized, controlled, parallel-group, observer-masked	SH ophthalmic solution 0.18% and HPMC/Dextran 70 eye drops; 1 drop of either product in each eye 6 times per day Ocular instillation	N=120 (11/109) SH 0.18%: n=60 (5/55) HPMC/ Dextran 70: n=60 (6/54)	Subjects with dry eye disease due to KCS or Sjögren's syndrome	60 days	Completed; Legacy study report
Safety and Efficacy	Rolando, 1994 (**4**)	To compare the effect of SH ophthalmic solution 0.18% and HPMC/Dextran 70 (Dacriosol®) eye drops on tear volume and tear stability; to evaluate the subsequent effect on tear mucus ferning and on the condition of ocular surface cells; and to assess the tolerability of the 2 formulations	Phase 2, randomized, controlled, parallel-group, observer-masked	SH ophthalmic solution 0.18% and HPMC/Dextran 70 eye drops; 1 drop of either product in each eye 6 times per day Ocular instillation	N=100 (92/8) SH 0.18%: n=50 (45/5) HPMC/ Dextran 70: n=50 (47/3)	Subjects with dry eye disease due to KCS or Sjögren's syndrome	60 days	Completed; Legacy study report

Abbreviations: F = Female; HPMC = Hydroxypropylmethylcellulose; KCS = Keratoconjunctivitis sicca; M = Male; SH = Sodium hyaluronate.

Continued

Table 1 (cont'd) Clinical Studies with Sodium Hyaluronate Ophthalmic Solution 0.18% (SVS20, Vismed®)

Type of Study	Study Identifier; Study Period	Objective(s) of the Study	Study Design and Type of Control	Treatment(s); Dosage Regimen; Route of Administration	No. of Subjects (M/F)	Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report
Safety and Efficacy	SVS20-99-02 Baudouin, 2001 (**5**)	To compare the performance of SH ophthalmic solution 0.18% to Celluvisc® in subjects with moderate dry eye disease and superficial keratitis	Phase 2 single-center, randomized, controlled, investigator-assessed, parallel-group	SH ophthalmic solution 0.18% and Celluvisc® eye drops; 1 drop of either product 3 times per day or as needed Ocular instillation	N=22 (21 completed); SH 0.18% n=10 (1/9) Celluvisc®: n=11 (0/11)	Subjects with moderate dry eye and superficial keratitis due to Sjögren's syndrome or diagnosed as primary syndrome	56 days	Completed; Full report
Efficacy	Johnson, 2008 (**6**)	To compare the efficacy of eye drops containing SH ophthalmic solution 0.18% to carbomer 934 0.3% (Lacryvisc®) in treating moderate dry eye disease	Phase 4, randomized, controlled, double-masked	SH ophthalmic solution 0.18% and carbomer 934 0.3% instilled in both eyes 2-8 times/day Ocular instillation	N=65 SH 0.18% n=32 carbomer 934 0.3%: n=33 M/F not specified in source document	Subjects with moderate dry eye disease	30 days	Completed; Published literature
Safety and Efficacy	SVS20-98-01 Rimmer, 2000 (**7**)	To determine the performance profile of SH ophthalmic solution 0.18% to include the evolution of the prelens tear film stability and symptoms in subjects with dry eye disease due to contact lens wear	Uncontrolled, exploratory study	SH ophthalmic solution 0.18%; 1 drop in each eye (single ocular instillation) while wearing contact lenses	N=10 (2/8)	Subjects with dry eye disease due to contact lens wear	1 instillation of 1 drop	Completed; Full report

Abbreviations: F = Female; KCS = Keratoconjunctivitis sicca; M = Male; SH = Sodium hyaluronate.

Continued

Table 1 (cont'd) Clinical Studies with Sodium Hyaluronate Ophthalmic Solution 0.18% (SVS20, Vismed®)

Type of Study	Study Identifier; Study Period	Objective(s) of the Study	Study Design and Type of Control	Treatment(s); Dosage Regimen; Route of Administration	No. of Subjects (M/F)	Diagnosis of Subjects	Duration of Treatment	Study Status; Type of Report
Efficacy	Montés-Micó, 2004 (**8**)	To determine changes in optical aberrations in subjects with dry eye disease before and after instillation of SH ophthalmic solution 0.18%	Uncontrolled, exploratory study	SH ophthalmic solution 0.18%; 1 drop Ocular instillation	N=15	Subjects with mild to moderate dry eye disease	1 instillation of 1 drop	Completed; Published literature
Efficacy	Patel, 2001 (**9**)	To evaluate the effectiveness of SH ophthalmic solution 0.18% in subjects with dry eye disease	Uncontrolled, exploratory study	SH ophthalmic solution 0.18%; 1 drop Ocular instillation	N=30	Subject with dry eye disease	1 instillation of 1 drop	Completed; Published literature
Safety and Efficacy	Prabhasawat, 2007 (**10**)	To evaluate the efficacy of SH 0.18% vs. HPMC 0.3%/Dextran 0.1% in subjects with evaporative tear-sufficient dry eye due to lipid tear deficiency	Phase 4, randomized, double-masked, controlled, exploratory	SH ophthalmic solution 0.18% and HPMC 0.3%/Dextran 0.1% eye drops; 1 drop of either product into each eye Ocular instillation	N=10 (20 eyes) (1/9)	Subjects with evaporative tear-sufficient dry eye due to lipid tear deficiency	1 instillation of 1 drop	Completed; Published literature

Abbreviations: F = Female; HPMC = Hydroxypropylmethylcellulose; KCS = Keratoconjunctivitis sicca; M = Male; SH = Sodium hyaluronate.

3.2 Summary of Clinical Development

Two Phase 3 studies, the results of which meet the regulatory standard of substantial evidence of safety and efficacy, support the approval of SH ophthalmic solution 0.18%: Study RP-001 (1), conducted by River Plate Biotechnology, Inc. and a study sponsored by TRB Chemedica, AG in Switzerland and conducted by Baudouin, et al (2005) (2) in multiple centers in France. These two studies evaluated a proprietary formulation of SH ophthalmic solution 0.18%. Study RP-001 was a Phase 3, multicenter, randomized, controlled, double-masked study to evaluate the product against its vehicle, and specifically investigated the unique contribution of SH to the vehicle solution. This study was designed to the replicate findings of a significant improvement in lissamine green staining and in symptom frequency score seen in the secondary endpoint analysis of the Baudouin 2005 study, which was also a multicenter, randomized, controlled, double-masked study that compared the drug product with a saline placebo.

In both studies, administration of SH ophthalmic solution 0.18% resulted in improvement of an objective sign (lissamine green staining score) and a subjective symptom (global symptom frequency score). It is important to note that improvement in signs and symptoms of dry eye disease were present in the comparison against a vehicle placebo (1), as well as a saline placebo (2). The analyses of the symptom intensity scores and the composite index of global symptom intensity and symptom frequency scores, plus the trend in the global impact of dry eye scores on the daily life questionnaire, are also supportive of the findings. The AEs reported were predominantly mild and were related to the underlying dry eye condition.

In addition to the two Phase 3 studies, four prospective, randomized, controlled clinical studies using SH ophthalmic solution 0.18% were conducted comparing it with commercially available tear substitutes: Dacriosol® (tear substitute with preservative) (3, 4); Celluvisc® (lubricant eye drop without preservative) (5), and Lacryvisc® (ophthalmic gel) (6). Improvement compared to baseline was observed in multiple objective signs and subjective symptoms in these studies, and the drug was well tolerated.

Finally, four single-instillation studies investigating tear film characteristics were conducted (7, 8, 9, 10). These studies, in addition to the pharmacodynamic findings of the studies conducted by Rapisarda (3) and Rolando (4), showed that SH ophthalmic solution 0.18% increased tear film stability and uniformity and decreased tear film osmolarity.

3.3 Communication with the Food and Drug Administration

In a series of meetings with the FDA, the Sponsor discussed the adequacy and relevance of the nonclinical and clinical study data that existed prior to conducting Study RP-001 (1). This section summarizes these meetings, highlighting the key agreements and the feedback that

was received with regard to the nonclinical and clinical data supporting the safety and efficacy of SH ophthalmic solution 0.18% for the treatment of the signs and symptoms of dry eye disease.

On August 2, 2006, a Pre-Phase 3 Meeting was held. The Agency agreed that the existing nonclinical data appeared sufficient to support an NDA, a carcinogenicity study would not be required, and that, of the seven clinical studies described in the pre-meeting package, the design of the Baudouin 2005 Phase 3 study (**2**) represented an adequate and well-controlled study. The sponsor submitted the study to the NDA based on the robust strength of certain objective and subjective secondary endpoints and with the intention to reproduce the results in the planned Phase 3 study, RP-001 (**1**).

In response to the proposed protocol for Study RP-001, the Agency suggested changes to the statistical analysis, which included the composition of the intent to treat (ITT) population and analysis of the per protocol (PP) population. The Agency requested the analysis of the primary endpoints in both the ITT and PP populations, using both the Wilcoxon rank sum test as the primary method of analysis and the Student's t-test as a supportive method of analysis.

The Sponsor subsequently submitted a request for an SPA for Study RP-001 (**1**). The Agency responded with some additional suggestions. A revised protocol was then submitted to the Agency for a final SPA, in which the following key study attributes were featured; the final Protocol was found to be acceptable as submitted:

- Study RP-001 was designed to have sufficient power to establish superiority of the product over vehicle, and cited two primary efficacy endpoints.

- The primary objective efficacy endpoint (sign) in the study eye was the mean change from baseline at Day 7 in lissamine green staining of the cornea, conjunctiva, and temporal conjunctiva, with each graded on a 0 to 4 scale (0 = 0%; 1 = 1%–15%; 2 = 16%–30%; 3 = 31% 45%; 4 = > 45%), for a maximum score of 12.

- The primary subjective efficacy endpoint (symptom) was the change from baseline at Day 7 in the summed scores for global symptom frequency in both eyes (soreness, scratchiness, dryness, grittiness, and burning), with each rated on a 0–3 scale (0 = Never; 1 = Sometimes; 2 = Often; 3 = Constantly), for a maximum score of 15.

- The primary efficacy endpoints were to be analyzed using the Wilcoxon rank sum test, supported by the Student's t-test. An alpha level of 0.025 (one-sided) was selected to determine statistical significance.

- Both primary endpoints (an objective sign and a subjective symptom) were required to reach statistical significance.

- The primary analysis of the endpoints for the study were to be conducted in the ITT population (all randomized subjects), using last observation carried forward (LOCF) data, which could include baseline data if non-baseline data were obtained.

- The superiority of SH ophthalmic solution 0.18% was to be established in both a primary objective endpoint, lissamine green staining scores, and a primary subjective endpoint, global symptom frequency scores.

4. Clinical Pharmacology

4.1 Introduction

No pharmacokinetic or absorption, distribution, metabolism, and elimination (ADME) studies have been performed in animals or humans using SH ophthalmic solution 0.18%; however, relevant results from pharmacokinetic and ADME studies with SH, the active ingredient in the product, are summarized in Section 4.2 below.

The pharmacodynamic properties of SH ophthalmic solution 0.18% were evaluated in nine clinical trials, including five comparative repeated-instillation studies evaluating tear volume, tear film stability, TBUT, and symptom intensity and frequency in subjects with dry eye due to KCS or Sjögren's syndrome (**2**, **3**, **4**, **5**) or moderate dry eye (**6**). Additionally, five single-instillation studies evaluated the effects of the product on TBUT, noninvasive break-up time (NIBUT), lipid layer thickness, symptom intensity and frequency, and/or ocular aberrations in subjects with symptomatic dry eye due to KCS, Sjögren's syndrome, or contact lens wear (**7**, **8**, **9**, **10**). These data are summarized in Section 4.3.

4.2 Pharmacokinetics and Absorption, Distribution, Metabolism, and Elimination

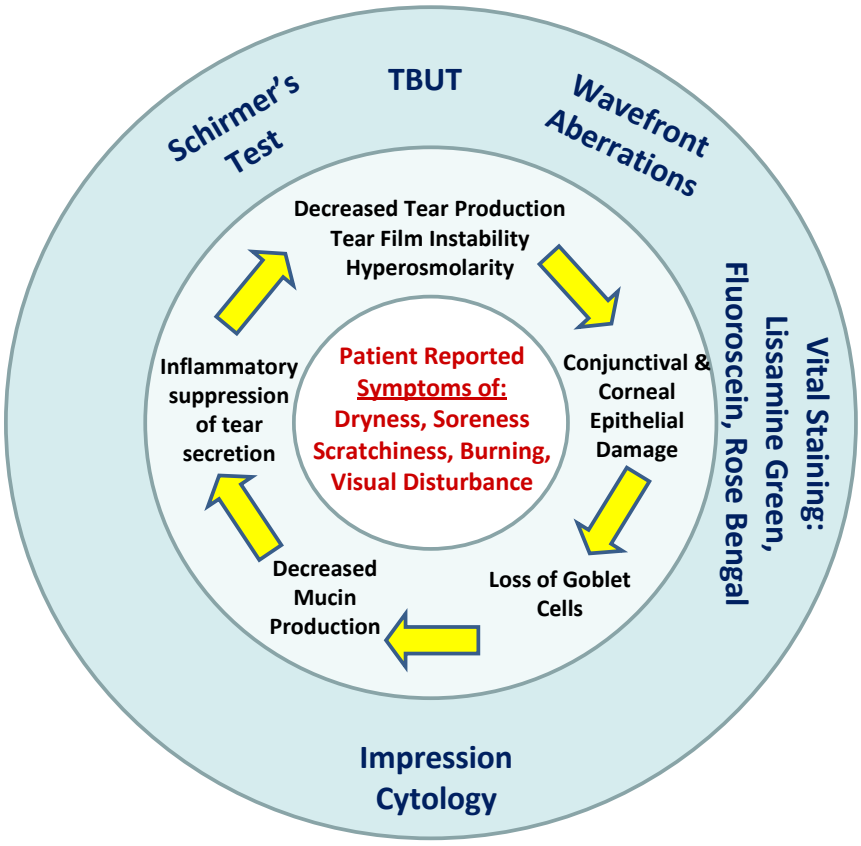
Extensive data are available for SH administered intra-articularly, intravenously, and intraocularly. Parenteral administration of SH results in rapid and efficient metabolism, rapid clearance from the blood, and degradation in the liver (Fraser, 1981 [cocks comb-derived SH]; Nimrod, 1992 [bacteria-derived SH]; Sakamoto, 1984 [cocks comb-derived SH]). Data from intraocular administration of bacteria-derived SH (molecular weight 2.8 million Daltons) in rabbits showed a slow disposition and followed first-order kinetics with an elimination half-life from the aqueous humour of 10.5 hours with no product detected 72 hours after administration (Nimrod, 1992).

Results from clinical studies with cocks comb-derived SH showed a prolonged residence time on the precorneal surface when SH was administered topically (Snibson, 1990). Based on extensive safety monitoring in animal and human studies, no clinically meaningful systemic absorption is expected (see Section 6.3).

4.3 Pharmacodynamics and Mechanism of Action

The primary causative mechanism of dry eye is a change in volume or composition of the tear film, which leads to its instability. Instability of the tear film causes the loss of ocular surface protection by the tears. The epithelial damage that occurs in patients with dry eye due to tear hyperosmolarity can lead to the loss of goblet cells, responsible for secreting mucins onto the ocular surface. The damage to the ocular surface and disruption of mucin production lead to further tear film instability. The instability further exacerbates the ocular surface hyperosmolarity. This circular cascade of events eventually leads to corneal erosion which is detected by the clinician via ocular staining with vital dyes such as lissamine green (Figure 3). The degree of vital staining correlates with the severity of damage to the cornea (Uchiyama, 2007).

Figure 3 Evaluation of Events Leading to Dry Eye



The time required for the tear film to dry and break exposing the ocular surface to drying after each blink is referred to as the tear film break-up time (TBUT). In a normal healthy eye, dry areas will occur between blinks at about 10-12 seconds, and an urge to blink is triggered. When TBUT is less than the blink rate, the ocular surface is left unprotected, and the signs

and symptoms of dry eye are exacerbated. The established TBUT limit for a diagnosis of dry eye is < 10 seconds (Lemp, 1973).

Tear film stability is critical for normal ocular health and was assessed in five comparative repeated-instillation studies (**2**, **3**, **4**, **5**, **6**) and four single-instillation studies of SH ophthalmic solution 0.18% (**7**, **8**, **9**, **10**). The five comparative studies with SH ophthalmic solution 0.18% and other ocular products showed that repeated instillations of SH ophthalmic solution 0.18% for up to 60 days improved the function and stability of the tear film in subjects with dry eye. Significant differences were observed among 120 subjects (**3**) and 100 subjects (**4**) who administered repeated instillations of SH ophthalmic solution 0.18% or the tear substitute Dacriosol® (HPMC 0.3%/Dextran 70 0.1%) for 60 days. Significantly increased TBUT and significantly increased tear volume were observed among subjects who administered SH ophthalmic solution 0.18% compared with those who administered HPMC 0.3%/Dextran 70 0.1%. Increased TBUT values from baseline were observed among 22 subjects who administered repeated instillations of SH ophthalmic solution 0.18% or the lubricant eye drop Celluvisc® (carboxymethylcellulose [CLV] 1%) for 56 days, with no significant difference noted between the 2 groups at any time point (**5**). Increased TBUT values were also observed among 151 subjects who administered repeated instillations of SH ophthalmic solution 0.18% or saline for 56 days, with no significant difference noted between the 2 groups at any time point (**2**). The values for TBUT and NIBUT did not show a statistically significant change from baseline for either SH ophthalmic solution 0.18% (Vismed®) or carbomer 934 0.3% (Lacryvisc®) in a study comparing the 2 compounds (**6**), perhaps indicating a lack of assay sensitivity in this study.

Similar significant improvements were observed in single-instillation studies in subjects with symptomatic dry eye. Significantly increased tear stability was observed at 5, 15, and 30 minutes postinstillation with effects lasting for 4 hours in subjects with dry eye due to contact lens wear (**7**), and observed at 15, 30, and 60 minutes postinstillation in subjects with evaporative tear-sufficient dry eye due to lipid tear deficiency (**10**). Tear film stability significantly increased from 4.9 ± 2.5 seconds to 13.0 ± 8.4 seconds postinstillation in subjects with dry eye due to KCS or Sjögren's syndrome (**9**).

Damage to the ocular surface and corneal deterioration can be observed via ocular staining with vital dyes. Fluorescein is used in conjunction with the TBUT test to visualize the tear break-up after a blink. Rose Bengal and lissamine green are also utilized to visualize the cornea. Lissamine green is a vital dye that, like fluorescein, stains corneal and conjunctival epithelial defects. Its main advantage lies in the fact that it stains keratinized and devitalized epithelial cells, goblet cells, mucus, and epithelial filaments, making it a more sensitive test than fluorescein. The loss of goblet cells is a hallmark of dry eye and can be readily assessed with lissamine green staining.

An improvement in ocular condition was observed among subjects with dry eye due to KCS or Sjögren's syndrome in two of the three comparative studies with repeated instillation of SH ophthalmic solution 0.18%. In one of the two comparative studies of the product and HPMC 0.3%/Dextran 70 0.1%, those subjects who administered the product had significantly reduced Rose Bengal and fluorescein staining, markedly improved conjunctival epithelial cell morphology, and increased number of goblet cells (**4**).

Impression cytology is a non-invasive method that lies between clinical and histological examination. A layer of cells from the conjunctival surface are collected and stained for protective cellular markers: CD44 (a known receptor for hyaluronic acid); CD63 (LAMP-3 lysosomal-membrane-associated glycoprotein, which acts as a protector of lysosomal membranes from digestion by hydrolytic enzymes [Fukuda, 1991]); UIC2 (P-glycoprotein acting as a membrane transporter and involved in xenobiotic efflux from the cell [Nagy, 2004]); and MUC5AC (a soluble mucin secreted by goblet cells [Pisella, 2004]). The presence of other cell surface proteins can indicate inflammation (HLA-DR, Class II human major histocompatibility complex antigen), which can exacerbate the cycle of corneal damage and irritation leading to deterioration, and apoptosis, which further worsens the inflammation by signaling the influx of immune modulating cells.

In the first of the two comparative studies comparing the product to CLV, SH ophthalmic solution 0.18% markedly increased expression of protective markers such as goblet cells, CD63, and UIC2, and decreased expression of CD44 (hyaluronic acid receptor), and HLA-DR inflammatory and apoptotic marker expression, indicating that the SH ophthalmic solution 0.18% provided greater protection of the ocular surface (**5**). In the second study, no significant differences were seen for either group in the protective markers MUC5AC, CD44, CD63, and UIC2 and the inflammatory marker HLA-DR (**2**). Eye drops with either carbomer or the product showed a similar statistically significant reduction in the extent of ocular surface staining in subjects with moderate dry eye (**6**).

The osmolarity of the tear film is critical for corneal epithelium health. Tear hyperosmolarity is a primary cause of discomfort and inflammation in dry eye (Lemp, 1995). Hyperosmolarity of the tears can lead to pathologic changes in the corneal epithelium such as increased desquamation, disrupted intercellular connections, disruptions in cell membranes, and cellular swelling with decreased cytoplasmic density (Gilbard, 1984). In animal studies, tear osmolarity was found to be a function of tear flow rate and evaporation, and the density of goblet cells decreased in the presence of hyperosmolarity (Gilbard, 1982).

Tear film osmolarity was evaluated in one of the comparative studies of SH ophthalmic solution 0.18% and HPMC 0.3%/Dextran 70 0.1% (**3**). A significant reduction in tear osmolarity to normal physiological limits was observed at 30 and 90 minutes postinstillation

among subjects treated with SH ophthalmic solution 0.18%, but no clinically appreciable reduction was observed among the subjects treated with HPMC 0.3%/Dextran 70 0.1%.

A smooth, intact, uniform tear film is essential for good visual acuity. The uniformity of the tear film after a single instillation of SH ophthalmic solution 0.18% was evaluated in 15 subjects with mild to moderate dry eye by assessing wavefront aberrations (**8**). Significant reductions in wavefront aberrations were observed for up to 10 minutes postinstillation. In another study, an apparent, but nonsignificant, change was observed in the thickness of the lipid layer over the precorneal tear film after a single instillation of SH ophthalmic solution 0.18% (**9**). In the Johnson study (**6**), more subjects experienced visual disturbance upon instillation of 1 minute or longer with the eye drops containing carbomer (48% [16/33]) than with the eye drops containing SH ophthalmic solution 0.18% (6% [2/32]), possibly due to a slightly higher viscosity of carbomer. Sodium hyaluronate ophthalmic solution 0.18% was well tolerated in these studies.

4.4 Conclusions

The causative mechanisms of dry eye are tear hyperosmolarity and tear film instability. Tear hyperosmolarity can cause damage to the surface of the epithelium. The epithelial damage involves cell death, particularly the loss of goblet cells, responsible for secreting mucins onto the ocular surface. The damage to the ocular surface and disruption of mucin production lead to further tear film instability. The instability exacerbates the ocular surface hyperosmolarity. Without therapeutic reversal of the damage, this ongoing cycle of dryness and irritation eventually leads to corneal deterioration.

Overall, the nine pharmacodynamic studies of SH ophthalmic solution 0.18% showed tear film stability was improved with single and repeated instillations of the solution, and furthermore, that repeated instillations re-established the health and stability of the ocular environment.

5. Clinical Efficacy

5.1 Overview of Clinical Studies

Ten studies assessed the efficacy of SH ophthalmic solution 0.18% in 512 subjects who were treated for up to 2 months. Seven of the studies were randomized and controlled (**1**, **2**, **3**, **4**, **5**, **6**, **10**) and three were uncontrolled and exploratory (**7**, **8**, **9**). The seven prospective, randomized, controlled clinical studies compared SH ophthalmic solution 0.18% with the following ocular products:

- Dacriosol® (HPMC/Dextran 70), a tear substitute with preservative (**3**, **4**);
- Bion Tears® (HPMC 0.3%/Dextran 0.1%), a tear substitute without preservative (**10**);
- Celluvisc® (CLV 1%), a lubricant eye drop without preservative (**5**);
- 0.9% sodium chloride (**2**);
- Lacryvisc® (carbomer 934 0.3%), a tear substitute without preservative (**6**); and
- Vehicle, a sterile hypotonic solution consisting of the excipients used in the product (**1**).

Results of the 10 studies evaluating clinical efficacy showed that the product is effective for treating the signs and symptoms of dry eye. Lissamine green staining scores, an indicator of the erosion of the ocular surface (cornea and conjunctiva), were significantly better in subjects treated with SH ophthalmic solution 0.18% than in subjects treated with placebo. The results from individual studies showed statistically significant benefits of SH ophthalmic solution 0.18% when compared with a placebo, or active control, in the following signs and symptoms: corneal staining (fluorescein and Rose Bengal), Schirmer's I test, TBUT, and impression cytology, global symptom frequency, visual analogue scale (VAS), composite index of symptoms, and the impact of dry eye on daily life.

This section presents the efficacy results from the clinical studies conducted with SH ophthalmic solution 0.18%, focusing mainly on comparing the efficacy results of the two Phase 3 studies (**1**, **2**) which meet the regulatory standard of substantial evidence of safety and efficacy and support approval of the NDA. These two studies showed that the SH ophthalmic solution 0.18% was significantly more effective than placebo (either saline or vehicle) when administered over a 14-day or 28-day treatment period, with an early onset of action observed at 7 days (Section 5.2). Brief narratives of the other well-controlled studies used to support efficacy are presented in Section 5.3. Efficacy assessments from the three uncontrolled studies were also supportive, but are not discussed here.

5.2 Phase 3 Studies: Baudouin 2005 and Study RP-001

5.2.1 Baudouin 2005 Study

A summary of the Baudouin 2005 protocol is provided in Appendix 10.3.1.

5.2.1.1 Primary Efficacy Endpoints

- Subjective Endpoint: Percent change from baseline of the final VAS summed score (sum of five VAS symptom scales for soreness, scratchiness, dryness, grittiness, and burning) at Day 28
- Objective Endpoint: Percent change from baseline of the final fluorescein staining summed score (sum of the total scores over both eyes) of the cornea at Day 28

5.2.1.2 Secondary Efficacy Endpoints

- Percent change from baseline in lissamine green staining of the cornea and nasal and temporal conjunctiva at Days 7 and 28
- Percent change from baseline in the slit lamp biomicroscopy signs at Days 7 and 28
- Percent change from baseline in tear prism height (mm) at Day 28
- Percent change from baseline in the tear volume (Schirmer's I test) at Days 7 and 28
- Percent change from baseline in TBUT at Days 7 and 28
- Mean percent change from baseline in flow cytometry parameters at Day 28
- Percent change from baseline in frequency of symptoms at Days 7 and 28
- Percent change from baseline in the composite index of symptom intensity on VAS and frequency at Days 7 and 28
- Percent change from baseline in the repercussion of symptoms on daily life activities at Days 7 and 28
- Frequency count (%) in the comfort of the eye drops at Days 7 and 28

This study, a randomized, double-masked, placebo-controlled, parallel-group, multicenter, Phase 3 investigation, assessed the efficacy of SH ophthalmic solution 0.18% versus 0.9% sodium chloride (saline placebo) in subjects with bilateral moderate dry eye. Subject disposition and demographics are summarized in Figure 4 and Table 2, respectively. In the study, 151 subjects (N = 74 active, N = 77 saline), were treated with 1 drop of SH ophthalmic solution 0.18% or saline in each eye 3 times per day or as needed up to 8 times per day for 28 days. Patients enrolled in this study were predominantly female (83.3%) and had a mean age of 61.6 ± 13.2 years. The randomized groups were similar with respect to age and gender. The majority of subjects (145/151; 96.0%) completed the study and the proportion of subjects who withdrew early from study treatment was equal for the two treatment groups. One subject in the saline group withdrew due to an AE.

Figure 4 Overview of Baudouin 2005 Patient Disposition

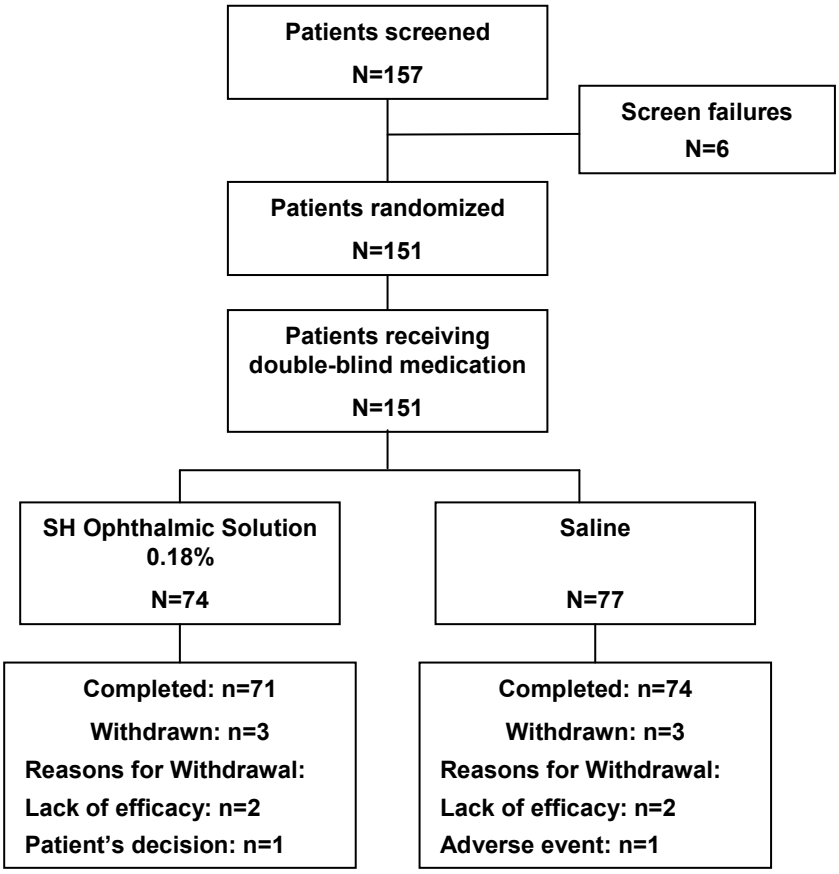


Table 2 Summary of Disposition and Demographic Data (ITT Population)

			Active (N=74)	Saline (N=77)
Disposition				
Completed the study			71 (95.9%)	74 (96.1%)
Subjects withdrawn early			3 (4.1%)	3 (3.9%)
Reason for early withdrawal				
	Lack of efficacy		2 (2.7%)	2 (2.6%)
	Patient's decision		1 (1.4%)	0
	Adverse event		0	1 (1.3%)
Demographics				
Age (years)		Mean (SD)	61.5 (13.9)	61.8 (12.6)
Gender				
	Male	n (%)	13 (17.6%)	12 (15.6%)
	Female	n (%)	61 (82.4%)	65 (84.4%)

Abbreviations: ITT = Intent to treat; N = Number of subjects in the ITT population in each treatment group, which is used as the denominator for all percentage calculations; SD = Standard deviation.

The results of the primary objective and subjective efficacy endpoints are summarized in Table 3. Statistical significance was evaluated against a one-sided alpha level of 0.025. The results of the secondary objective and subjective efficacy endpoints are summarized in Table 4.

Table 3 Baudouin 2005 Results for the Primary Objective and Subjective Endpoints (ITT Population)

Measure	Visit	Study Drug	Mean (SD)	*P* Value[a]
Fluorescein staining of cornea[b]	Day 7	Active	-27.03 (38.36)	0.0546
		Saline	-20.19 (38.26)	
	Day 28[c]	Active	-43.44 (47.21)	0.0279
		Saline	-30.21 (44.75)	
VAS summed score[b]	Day 7	Active	-19.85 (28.2)	0.0300
		Saline	-16.17 (27.03)	
	Day 28[c]	Active	-33.98 (32.0)	0.1337
		Saline	-31.23 (32.68)	

Abbreviations: ITT = Intent to treat; SD = Standard deviation; VAS = Visual analogue scale.

a. Wilcoxon-Mann-Whitney test with an alpha level of 0.025

b. Results are expressed as percent change from baseline.

c. Day 28 was the primary endpoint.

Table 4 Baudouin 2005 Results for the Secondary Objective and Subjective Endpoints (ITT Population)

Measure	Visit	Study Drug	Mean (SD)	*P* Value[a]
Lissamine green staining[b]	Day 7	Active	-28.32 (34.48)	**0.0013**
		Saline	-13.62 (41.81)	
	Day 28	Active	-41.18 (31.24)	**0.0007**
		Saline	-22.97 (39.60)	
Frequency of symptoms[b]	Day 7	Active	-23.28 (33.03)	**0.0117**
		Saline	-13.50 (30.60)	
	Day 28	Active	-34.86 (26.38)	**0.0035**
		Saline	-22.83 (34.68)	
Composite index of symptom intensity on VAS and frequency[b]	Day 7	Active	-33.17 (52.35)	0.0440
		Saline	-20.09 (48.00)	
	Day 28	Active	-53.60 (30.93)	**0.0222**
		Saline	-33.85 (57.31)	
Repercussion of symptoms on daily life activities[b]	Day 7	Active	-15.26 (39.52)	**0.0235**
		Saline	-5.63 (34.26)	
	Day 28	Active	-33.10 (33.51)	**0.0053**
		Saline	-17.53 (42.91)	
Measure	**Visit**	**Study Drug**	**Frequency Count (%)**	***P* Value[a]**
Comfort of eye drops	Day 28	Active	Good 83.10	**0.0158**
			Moderate 15.49	
			Bad 1.41	
		Saline	Good 70.27	
			Moderate 13.51	
			Bad 16.22	

Abbreviations: ITT = Intent to treat; SD = Standard deviation; VAS = Visual analogue scale.

a. Wilcoxon-Mann-Whitney test with an alpha level of 0.025

b. Results are expressed as percent change from baseline.

Note: Bolded *P* values denote statistical significance in favor of SH ophthalmic solution 0.18%.

In the original analysis of the Baudouin 2005 study, the primary objective endpoint (change from baseline in final summed score of fluorescein staining of the cornea at Day 28) and subjective endpoint (percent change from baseline in the final VAS summed score at Day 28) did not reach significance (Table 3). However, results of staining with lissamine green were highly supportive in favor of SH ophthalmic solution 0.18% at both Day 7 ($P = 0.0013$) and Day 28 ($P = 0.0007$) (Table 4). At Day 7, the mean decrease in staining score was 28.32% in the active group and 13.62% in the saline group. At Day 28, mean decrease in staining score was 41.18% versus 22.97%, respectively.

Supportive trends in favor of SH ophthalmic solution 0.18% over saline were found in the values of percent change from baseline in symptoms frequency at both Day 7 (-23.28% and -13.50%, respectively; $P = 0.0117$) and Day 28 (-34.86% and -22.83%, respectively; $P = 0.0035$) (Table 4). The difference between active and saline for the composite index of symptom intensity and frequency (53.60% and 33.85% reduction, respectively) was supportive ($P = 0.0222$) in favor of SH ophthalmic solution 0.18% at Day 28. The difference for the percent change from baseline in repercussion of symptoms on daily life activities at both Day 7 (15.26% decrease for the active group and 5.63% decrease for the saline group; $P = 0.0235$) and Day 28 (33.10% and 17.53% decrease, respectively; $P = 0.0053$) were supportive of SH ophthalmic solution 0.18%. A supportive trend favoring SH ophthalmic solution 0.18% was observed at Day 28 for comfort of the eye drops ($P = 0.0158$).

Though statistically significant differences were not found for symptoms intensity on VAS, corneal staining with fluorescein, slit lamp examination, TBUT, tear prism height, and tear volume, all measures showed a percent change from baseline that was higher in the SH ophthalmic solution 0.18% group than in the saline group (data not shown) for these endpoints.

Safety was assessed by slit lamp examination, best corrected visual acuity (BCVA), AE reporting, and examination of ocular adnexa. The incidence of AEs was similar in the SH ophthalmic solution 0.18% group (N = 74, 13.5%) and the saline group (N = 77, 11.7%). The most common AEs reported were ocular burning in the SH ophthalmic solution 0.18% group (2.7%) and headache in the saline group (2.6%). No severe AEs were reported in either group. Ophthalmic AEs were reported in both the SH ophthalmic solution 0.18% group (4.0%) and the saline group (6.5%). The proportion of AEs considered by the investigator to be possibly or probably related to study drug was slightly higher in the saline group compared with the SH ophthalmic solution 0.18% group (4.0% and 1.3%, respectively). There were no serious AEs (SAEs) reported.

Results of this study, suggested that SH ophthalmic solution 0.18% was potentially effective, safe, and well tolerated in subjects with moderate dry eye disease.

To support the study design and selection of endpoints in Study RP-001 (**1**), a reanalysis of the raw efficacy datasets from Baudouin 2005 was performed. The study population in Baudouin 2005 was broad and inconsistent with the more restrictive definition of dry eye the Sponsor proposed to study in RP-001. Therefore, the population of subjects to be included in the reanalysis was adjusted accordingly.

The subset of subjects from the Baudouin 2005 Phase 3 study reanalysis was representative of a subject population to be targeted in the subsequent Study RP-001, providing a study

design that would replicate the results of key endpoints in the Baudouin 2005 study. In the reanalysis, all efficacy endpoints were analyzed to determine the endpoints most appropriate for inclusion in the confirmatory study and to determine the most robust among them as efficacy endpoints for replication. Last observation carried forward methods were used to assess the impact of missing values on primary and secondary endpoints.

The results of the reanalysis of the Baudouin 2005 study revealed that in this population of subjects, SH ophthalmic solution 0.18% was superior to saline in percent change from baseline for both lissamine green staining and composite index of symptom intensity and frequency (Table 8).

5.2.2 Study RP-001

A summary of the RP-001 protocol is provided in Appendix 10.3.2.

5.2.2.1 Primary Efficacy Endpoints

- Objective Endpoint: Change from baseline in summed scores of lissamine green staining of the cornea and nasal and temporal conjunctiva at Day 7
- Subjective Endpoint: Change from baseline in summed global symptom (soreness, scratchiness, dryness, grittiness, burning) frequency scores at Day 7

5.2.2.2 Secondary Efficacy Endpoints

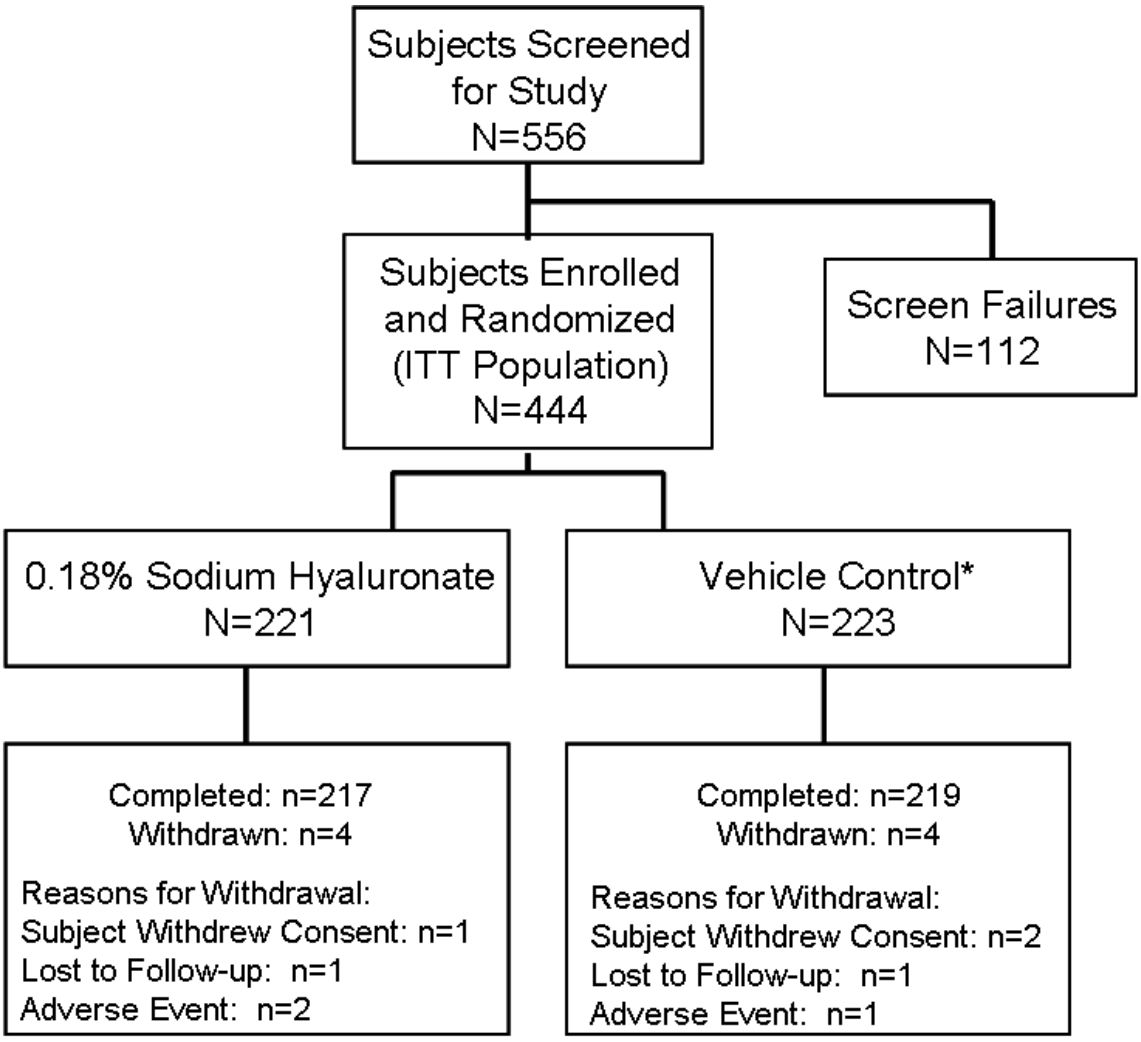
- Change from baseline in summed lissamine green staining scores at Day 14
- Change from baseline in summed global symptom frequency scores at Day 14
- Percent change from baseline in summed scores for fluorescein corneal staining at Days 7 and 14
- Percent change from baseline in the Schirmer's I test scores at Days 7 and 14
- Percent change from baseline in summed VAS symptom scores scale at Days 7 and 14
- Percent change from baseline in composite index of global symptom intensity and symptom frequency score at Days 7 and 14
- Percent change from baseline in rating the impact of dry eye syndrome on daily life (eg, screen work, television viewing, reading, and driving) at Days 7 and 14

This Phase 3, multicenter, randomized, placebo-controlled, double-masked trial compared the efficacy and safety of SH ophthalmic solution 0.18% with its vehicle for the treatment of the signs and symptoms of dry eye disease.

Subject disposition and demographics are summarized in Figure 5 and Table 5, respectively. A total of 444 subjects were enrolled and treated (active: N = 221, vehicle: N = 223). Of these, 333 (75%) subjects were female and the mean age (± SD) of all subjects was 61.5 ± 13.7 years. The randomized groups were similar with respect to age, gender, ethnicity, and race. The majority of subjects (436/444; 98.2%) completed the study and the proportion

of subjects who withdrew early from study treatment was equal for the two treatment groups. A total of three subjects (active: 2/221 [0.9%]; vehicle: 1/223 [0.4%]) withdrew due to an AE. None of the subjects' treatment assignments were unmasked during the study.

Figure 5 Overview of RP-001 Subject Disposition



* One subject in the Vehicle Control group withdrew consent prior to instilling the study drug, and therefore was excluded from the safety population analysis (N=443; active: n=221; vehicle: n=222).

Table 5 Summary of Disposition and Demographic Data (ITT Population)

			Active (N=221)	Vehicle (N=223)	Overall (N=444)
Disposition					
Completed the study			217 (98.2%)	219 (98.2%)	436 (98.2%)
Subjects withdrawn early			4 (1.8%)	4 (1.8%)	8 (1.8%)
Reason for early withdrawal					
	Subject withdrew consent		1 (0.5%)	2 (0.9%)	3 (0.7%)
	Lost to follow		1 (0.5%)	1 (0.4%)	2 (0.5%)
	Adverse event		2 (0.9%)	1 (0.4%)	3 (0.7%)
Demographics					
Age (years)		Mean (SD)	60.7 (12.6)	62.2 (14.8)	61.5 (13.7)
Gender					
	Male	n (%)	49 (22.2%)	62 (27.8%)	111 (25.0%)
	Female	n (%)	172 (77.8%)	161 (72.2%)	333 (75.0%)
Ethnicity					
	Hispanic or Latino	n (%)	17 (7.7%)	14 (6.3%)	31 (7.0%)
	Not Hispanic or Latino	n (%)	204 (92.3%)	209 (93.7%)	413 (93.0%)
Race					
	White	n (%)	192 (86.9%)	188 (84.3%)	380 (85.6%)
	Black/African American	n (%)	20 (9.0%)	30 (13.5%)	50 (11.3%)
	American Indian/Alaskan Native	n (%)	1 (0.5%)	0	1 (0.2%)
	Asian	n (%)	3 (1.4%)	2 (0.9%)	5 (1.1%)
	Other	n (%)	5 (2.3%)	3 (1.3%)	8 (1.8%)

Abbreviations: ITT = Intent to treat; N = Number of subjects in the ITT population in each treatment group, which is used as the denominator for all percentage calculations; SD = Standard deviation.

The data in the study were analyzed by Wilcoxon rank sum test, which is appropriate for ordinal data, and Student's t-test. As discussed by Shuster (2005), the t-test is also valid and appropriate for ordinal data such as those collected for the primary objective and subjective endpoints. The results obtained by the two statistical methods, Wilcoxon and Student's t-test, support each other in this study. Analysis using the van Elteren test and the cumulative distribution of the change score from baseline reinforced the data obtained for the primary endpoints. In particular, the superiority of SH ophthalmic solution 0.18% was established in both a primary objective endpoint, lissamine green staining scores, and a primary subjective endpoint, global symptom frequency scores. The trend observed in treatment effects in secondary objective and subjective efficacy endpoints at Day 7 and/or Day 14 demonstrated the beneficial effects of SH ophthalmic solution 0.18% at and beyond the initial (7 day)

endpoint observation, providing additional reinforcement to the findings in the primary endpoints.

The results of the primary objective and subjective efficacy endpoints are summarized in Table 6. Statistical significance was evaluated against a 2-sided alpha level of 0.05. At Day 7, the difference of the means in the change from baseline between the active and vehicle arms for lissamine green staining scores (objective) was statistically significant in the ITT population with LOCF using the t-test (active: -1.1, vehicle: -0.7; $P = 0.0291$) and essentially significant using the Wilcoxon rank sum test ($P = 0.0502$). The decrease from baseline in lissamine green staining in the SH ophthalmic solution 0.18% group was 57% greater than the decrease in the vehicle group, calculated as ([1.1-0.7] ÷ 0.7) x 100. At Day 7, the difference in means in the change from baseline between active and vehicle arms for the global symptom frequency score (subjective) was statistically significant for the ITT population with LOCF (active: -1.7, vehicle: -1.1; $P = 0.0173$ [t-test], $P = 0.0497$ [Wilcoxon]). The decrease from baseline in the global symptom score in the SH ophthalmic solution 0.18% group was 54.5% greater than the decrease in the vehicle group, calculated as ([1.7-1.1] ÷ 1.1) x 100.

The *P*-values for the van Elteren test (Lehmann, 1975), which is a version of the Wilcoxon test that employs adjustment for site in a manner that is comparable to a two-way analysis of variance, were also calculated for both primary endpoints. As shown in Table 6, the van Elteren test *P*-values were somewhat smaller than the corresponding unstratified Wilcoxon *P*-values and were confirmatory of the observations found in the primary endpoints analyses.

Table 6 Study RP-001 Results for the Primary Objective and Subjective Endpoints at Day 7 (ITT Population with LOCF)

Measure	Visit	Study Drug	Mean (SD)	*P* Value Student's t-test[a,b]	*P* Value Wilcoxon rank sum test[b]	*P* Value van Elteren[b]
Lissamine green staining	Day 0	Active	5.71 (2.421)	0.4132	0.4157	-
		Vehicle	5.52 (2.357)			
	Day 7	Active	-1.1 (2.01)	**0.0291**	**0.0502**	**0.0354**
		Vehicle	-0.7 (1.79)			
Global symptom frequency	Day 0	Active	8.33 (2.231)	0.6208	0.3865	-
		Vehicle	8.22 (2.470)			
	Day 7	Active	-1.7 (2.78)	**0.0173**	**0.0497**	**0.0451**
		Vehicle	-1.1 (2.62)			

Abbreviations: ITT = Intent to treat; LOCF = Last observation carried forward; SD = Standard deviation.

a. Student's t-test p-values were confirmed by permutation test p-values.

b. Alpha level of significance of 0.050 (two-sided)

These results are supportive of the observed statistically significant differences between active and vehicle treatments reported above. Treatment effects were noted in several secondary objective and subjective efficacy endpoints. At Day 14, the difference in means from baseline for lissamine green staining scores in the active and vehicle arms for the ITT population with LOCF were: active -1.4; vehicle -1.0; $P = 0.0243$ (t-test) and $P = 0.0461$ (Wilcoxon).

At Day 7, SH ophthalmic solution 0.18% was superior in the mean summed VAS symptoms intensity scores (active: -22.81, vehicle:-14.91; $P = 0.0301$). This was also true for the mean percent change from baseline in the composite index of global symptom intensity and global symptom frequency scores at Day 7 (active: -31.36, vehicle: -18.73; $P = 0.0095$).

The Global Impact of Dry Eye on Daily Life at baseline demonstrated that the majority of subjects reported an impact of dry eye on their daily life. Approximately 10% more subjects in the active arm compared with the vehicle arm reported an improvement of at least 1 grade at Day 7, and about 7% more reported this at Day 14 (Table 7).

Table 7 Study RP-001 Results for Global Impact of Dry Eye on Daily Life at Day 7 and Day 14 (ITT Population with LOCF)

Study Drug	% Reporting a Global Impact at Baseline	% Reporting Improvement by 1 or more Grades	
		Day 7	Day 14
Active	55.7%	40.3%	50.3%
Vehicle	53.4%	30.4%	43.4%

Abbreviations: ITT = Intent to treat; LOCF = Last observation carried forward.

To better understand the beneficial effect of treatment over the vehicle at Day 7, in the population studied, the cumulative distributions of the change scores from baseline in the primary endpoints are provided in Figure 6.

Figure 6 Cumulative Distributions of Primary Endpoints (ITT Population)

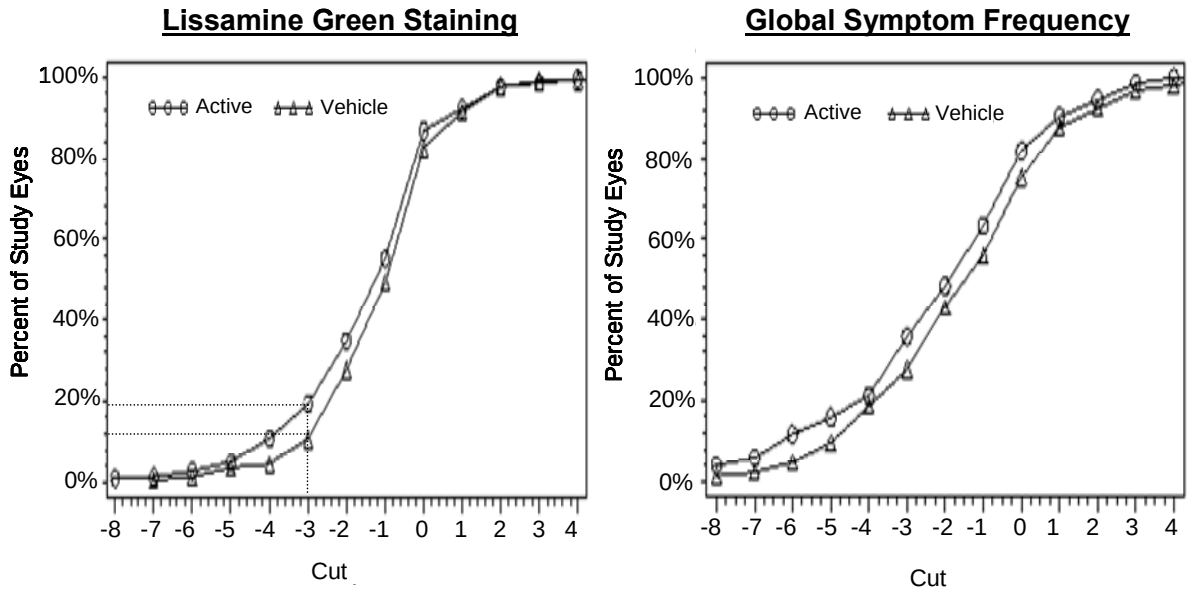


Figure 6 shows the cumulative proportion of study eyes achieving a change score that reached a specified threshold or "cut" (ie, the number of scale units decreased from baseline). For example, in Figure 6 (left) for lissamine green staining, the active group in the ITT population with LOCF 19% of the study eyes achieved a change score from baseline of ≤ -3, while only 11% in the vehicle group met this condition. Separation of the active group from the vehicle group is depicted by the curves of the two endpoints, showing that the distributions for the active group (objective and subjective endpoints) were all shifted consistently to the left of their counterparts for the vehicle group, indicating a higher

proportion of eyes showing treatment effects of SH ophthalmic solution 0.18% solution compared with the effect of the vehicle.

The safety population for this study included all subjects who were administered at least 1 dose of study drug (overall: N = 443; active: N = 221; vehicle: N = 222). One subject in the vehicle group withdrew consent prior to instilling the study drug, and therefore was excluded from the safety population analysis. Approximately 25% of subjects in each treatment group reported an AE (active: 57/221, 25.8%; vehicle: 48/222, 21.6%).

The most frequent AEs in both treatment groups were dry eye (active: 18/221, 8.1%; vehicle: 14/222, 6.3%), eye pain (active: 13/221, 5.9%; vehicle: 7/222, 3.2%), and foreign-body sensation (active: 5/221, 2.3%; vehicle: 7/222, 3.2%). There was 1 SAE reported in each treatment group. Both SAEs were considered unrelated to the study drug. Three subjects (active: 2/221, 0.9%; vehicle: 1/222, 0.05%) withdrew from the study due to AEs. There were no significant changes from baseline in the slit lamp examinations, BCVA, intraocular pressure (IOP), or dilated fundus examination variables. Overall, there were no clinically important safety findings related to the use of the active study drug, which appeared to be well tolerated.

5.2.3 Integrated analysis

5.2.3.1 Endpoints for Efficacy Evaluation in the Integrated Analysis

Standard clinical assessments of the severity of dry eye disease were performed in both studies. The protocol for Study RP-001 was designed to be comparable with the Baudouin 2005 study with regard to endpoints and analysis methodology. The primary objective and subjective endpoints for Study RP-001 were selected to reproduce the demonstrations of efficacy for the same *sign*, lissamine green staining scores, and the same composite of dry eye *symptoms* (soreness, scratchiness, dryness, grittiness, and burning) as those achieved in the Baudouin 2005 study, where these were secondary endpoints, with robust strength. The control for the Baudouin 2005 study was saline, whereas the control in Study RP-001 was the vehicle.

The objective and subjective endpoints common to both the Baudouin 2005 study and Study RP-001 are presented in the following sections. The study results are presented with an emphasis on the integrated analysis of the primary and secondary endpoints achieved in both studies. Of the primary and secondary endpoints described for the Baudouin 2005 study, the following were evaluated in Study RP-001 as primary endpoints, using identical or similar analytical methods:

- Change from baseline in lissamine green staining of the cornea and nasal and temporal conjunctiva at Days 7 and 28; analyzed as a percent change in Baudouin 2005. The integrated analysis harmonizes the results expressed as "change from baseline."
- Change from baseline in frequency of symptoms at Days 7 and 28; calculated as a percent change in Baudouin 2005. The integrated analysis harmonizes the results expressed as "change from baseline."

5.2.3.2 Study Populations and Demographics

In the Baudouin 2005 study, subjects had ≥ 3 month documented history of bilateral moderate dry eye diagnosed as a primary condition (KCS) or secondary to Sjögren's syndrome. Subjects with severe dry eye (ie, corneal staining with fluorescein with a depth score ≥ 3 and/or severe conjunctival hyperemia and/or severe blepharitis) were excluded from enrollment in the Baudouin 2005 study. In Study RP-001, subjects were eligible for enrollment if they had ≥ 3 month documented history of bilateral dry eye diagnosed as dry eye, KCS, or due to Sjögren's syndrome. In both studies, eligible subjects were at least 18 years of age. The Baudouin 2005 study was conducted at clinical sites in France, while Study RP-001 was conducted at clinical sites in the US.

In both the Baudouin 2005 and RP-001 studies, subject demographics were well balanced between the treatment groups. In the Baudouin 2005 study, across the treatment groups, there were more females (83.4%) than males (16.6%), and subjects ranged in age from 28 to 88 years. Race was not captured in this study. In Study RP-001, across the treatment groups, there were also more females (75%) than males (25%), the age range was 21 to 92 years, and the majority of subjects were White (85.6%).

5.2.3.3 Subject Disposition

In the Baudouin 2005 study, the total number of subjects included in the ITT population was 151 (SH ophthalmic solution 0.18%: N = 74; saline: N = 77). The percentage of subjects who completed the study was comparable between the 2 treatment groups (SH ophthalmic solution 0.18%: 97.3%; saline: 96.1%). In Study RP-001, 444 subjects were included in the ITT population (SH ophthalmic solution 0.18%: N = 221; vehicle: N = 223). The percentage of subjects who completed the study was identical between the 2 treatment groups (98.2% in

each treatment group). Across both studies, none of the subjects in the SH ophthalmic solution 0.18% groups withdrew due to lack of efficacy, and withdrawals due to AEs in the SH ophthalmic solution 0.18% groups were reported for 1 subject (1.4% [1/74]) in the Baudouin 2005 study and 2 subjects (0.9% [2/77]) in Study RP-001.

5.2.3.4 Statistical Methodology

To support an effective integrated analysis of the efficacy results of the two similar, but not identical studies, the original data from the Baudouin 2005 study were re-analyzed to conform to an analysis plan consistent with the analysis of Study RP-001. To achieve consistency between the data from the two studies, the Baudouin 2005 study data were adjusted to designate a study eye for the objective endpoint and to re-analyze the data by "change from baseline" as opposed to the original analysis which was performed as "percent change from baseline." Results from the integration of the re-analyzed Baudouin 2005 study and Study RP-001 were reported using descriptive statistics: number of subjects (N), mean, standard deviation or standard error of the mean, median, maximum, and minimum for continuous outcomes and frequency and percentage for categorical variables at each assessment time point, except for the exposure analyses.

Change from baseline for efficacy endpoints was reported by treatment group for each applicable time point. LOCF analyses included the baseline observation if no non-baseline measurements were available. Whenever an LOCF analysis was performed in a specified analysis population, an observed cases analysis was also performed.

The analysis variable for the primary objective endpoint, lissamine green staining, was the study eye and that for the primary subjective efficacy endpoint, global symptom frequency score, was both eyes. For Study RP-001, the eye with the lower Schirmer's I test score at baseline ("worse" eye) was designated as the study eye. If both eyes were equal, the right eye was to be designated as the study eye. The Baudouin 2005 study did not specify a study eye, however for the integrated analysis, the study eye was designated retrospectively using the same criteria as defined in Study RP-001 (ie, the eye with the lower Schirmer's I test score ["worse" eye]).

The primary subjective endpoint, global symptom frequency score, is a composite score. In both studies, subjects rated the frequency of 5 individual symptoms (burning, scratchiness, grittiness, dryness, and soreness) on a scale where 0 = never, 1 = sometimes, 2 = often, and 3 = constantly. The subjects selected a single value on both eyes together for each of the 5 symptoms. The global score is the sum of the 5 scores for a maximum total of 15.

Change from baseline and percent change from baseline were tested using the Wilcoxon rank sum test. A t-test and analysis of covariance (ANCOVA) stratified on center with baseline as

a covariate was also carried out. Treatment-by-center interaction in the ANCOVA was also assessed. A type I error rate of 0.05 (two-sided) was used when assessing statistical significance.

The ITT population was defined as all randomized subjects. An ITT analysis with LOCF for missing data was conducted for all efficacy endpoints. The total number of subjects in the comparison of the efficacy results of the integrated ITT population was 295 subjects in the SH ophthalmic solution 0.18% groups (Baudouin 2005: N = 74; Study RP-001: N = 221) and 299 subjects in the control (saline or vehicle) groups (Baudouin 2005: N = 77; Study RP-001: N = 223).

5.2.3.5 Efficacy Results of the Two Phase 3 Studies Meeting the Regulatory Standard of Substantial Evidence of Safety and Efficacy

5.2.3.5.1 Efficacy in Primary Objective and Subjective Endpoints

5.2.3.5.1.1 Primary Objective Efficacy Endpoint: Lissamine Green Staining Scores at Day 7

In the re-analysis of the Baudouin 2005 study results, the change from baseline in lissamine green staining scores was statistically significantly greater for the SH ophthalmic solution 0.18% group versus the saline group at Day 7 ($P = 0.0157$ [Wilcoxon]; $P = 0.0237$ [t-test]) (Table 8). The mean changes from baseline were -1.1 for the active group and -0.6 for the saline group, and the median change from baseline was -1.0 for the active group and 0.0 for the saline group.

In Study RP-001, the change from baseline for lissamine green staining scores in the ITT population with LOCF applied was essentially significant using the Wilcoxon rank sum test ($P = 0.0502$) and statistically significant using the t-test ($P = 0.0291$) (Table 8). The mean changes from baseline at Day 7 were -1.1 for the active group and -0.7 for the vehicle group. The median changes from baseline at Day 7 were -1.0 for the active group and 0.0 for the vehicle group.

Table 8 Lissamine Green Staining Scores (ITT Population with LOCF)

Visit [a]	Treatment [b]	Baudouin 2005				Study RP-001			
		Mean (SD)	Median	*P* value Wilcoxon Rank Sum Test [c]	*P* value Student's t-test [c]	Mean (SD)	Median	*P* value Wilcoxon Rank Sum Test [c]	*P* value Student's t-test [c]
Day 0	SH Ophthalmic Solution 0.18%	4.03 (2.120)	4.00	0.4283	0.5857	5.71 (2.421)	5.00	0.4157	0.4132
	Saline/Vehicle	3.83 (2.279)	3.00			5.52 (2.357)	5.00		
Day 7	SH Ophthalmic Solution 0.18%	-1.1 (1.51)	-1.0	**0.0157**	**0.0237**	-1.1 (2.01)	-1.0	**0.0502**	**0.0291**
	Saline/Vehicle	-0.6 (1.38)	0.0			-0.7 (1.79)	0.0		
Day 14/28	SH Ophthalmic Solution 0.18%	-1.6 (1.67)	-2.0	**0.0131**	**0.0144**	-1.4 (1.91)	-1.0	**0.0461**	**0.0243**
	Saline/Vehicle	-0.9 (1.46)	-1.0			-1.0 (1.81)	-1.0		

Abbreviations: ITT = Intent to treat; LOCF = Last observation carried forward; SD = Standard deviation; SH = Sodium hyaluronate.

a. Day 14 was analyzed for efficacy in Study RP-001 and Day 28 in the Baudouin 2005 study.
b. Saline was the control in the Baudouin 2005 study and vehicle was the control in Study RP-001.
c. Alpha level of significance of 0.05 (two-sided)

5.2.3.5.1.2 Primary Subjective Efficacy Endpoint: Global Symptom Frequency Scores at Day 7

In the re-analysis of the Baudouin 2005 study, statistically significantly greater changes from baseline in global symptom frequency scores were observed for the SH ophthalmic solution 0.18% versus the saline groups at Day 7 (P = 0.0372 [Wilcoxon]); P = 0.0470 [t-test]) (Table 9). At Day 7, the mean changes from baseline were -2.0 for the SH ophthalmic solution 0.18% group and -1.2 for the saline group. The median changes from baseline were -2.0 for the SH ophthalmic solution 0.18% group and -1.0 for the saline group.

In Study RP-001, the changes from baseline in global symptom frequency scores at Day 7 revealed mean and median changes from baseline that were statistically significant (P = 0.0497 [Wilcoxon]; P = 0.0173 [t-test]) (Table 9). The mean changes from baseline at Day 7 were -1.7 for the SH ophthalmic solution 0.18% group and -1.1 for the vehicle group. The median changes from baseline were -1.0 for the SH ophthalmic solution 0.18% group and -1.0 for the vehicle group.

Table 9 Global Symptom Frequency Scores (ITT Population with LOCF)

Visit [a]	Treatment [b]	Baudouin 2005				Study RP-001			
		Mean (SD)	Median	*P* value Wilcoxon Rank Sum Test [c]	*P* value Student's t-test [c]	Mean (SD)	Median	*P* value Wilcoxon Rank Sum Test [c]	*P* value Student's t-test [c]
Day 0	SH Ophthalmic Solution 0.18%	8.35 (2.272)	8.00	0.2442	0.3477	8.33 (2.231)	8.00	0.3865	0.6208
	Saline/Vehicle	8.04 (1.758)	8.00			8.22 (2.470)	8.00		
Day 7	SH Ophthalmic Solution 0.18%	-2.0 (2.44)	-2.0	**0.0372**	**0.0470**	-1.7 (2.78)	-1.0	**0.0497**	**0.0173**
	Saline/Vehicle	-1.2 (2.58)	-1.0			-1.1 (2.62)	-1.0		
Day 14/28	SH Ophthalmic Solution 0.18%	-2.9 (2.29)	-3.0	**0.0127**	**0.0134**	-2.4 (2.91)	-2.0	0.3136	0.2202
	Saline/Vehicle	-1.8 (2.81)	-2.0			-2.1 (2.92)	-2.0		

Abbreviations: ITT = Intent to treat; LOCF = Last observation carried forward; SD = Standard deviation; SH = Sodium hyaluronate.

a. Day 14 was analyzed for efficacy in Study RP-001 and Day 28 in the Baudouin 2005 study.
b. Saline was the control in the Baudouin 2005 study and vehicle was the control in Study RP-001.
c. Alpha level of significance of 0.05 (two-sided)

5.2.3.5.2 Efficacy in Secondary Endpoints

5.2.3.5.2.1 Lissamine Green Staining Scores at Day 14/Day 28

In the re-analysis of the Baudouin 2005 study, the changes from baseline in lissamine green staining scores were supportive for the SH ophthalmic solution 0.18% group versus the saline group at Day 28 ($P = 0.0131$ [Wilcoxon]; $P = 0.0144$ [t-test]) (Table 8). The mean changes from baseline at Day 28 were -1.6 for the active group and -0.9 for the saline group. The median changes from baseline at Day 28 were -2.0 for the active group and -1.0 for the saline group.

In Study RP-001, the benefit of SH ophthalmic solution 0.18% over vehicle in significantly reducing lissamine green staining scores at Day 7 was sustained through Day 14 ($P = 0.0461$ [Wilcoxon]; $P = 0.0243$ [t-test]) (Table 8). The mean changes from baseline at Day 14 were -1.4 for the active group and -1.0 for the vehicle group. The median changes from baseline on Day 14 were -1.0 for both the active and vehicle groups.

5.3 Summary of Well-Controlled Studies not Included in the Integrated Efficacy Analysis

Five controlled studies were not included in the integrated analyses because of lack of double-masking or primary endpoints dissimilar to those in the two Phase 3 studies. Additionally, two of the studies used active controls rather than benign placebos (saline and vehicle) as did the other studies included in the integrated analyses.

5.3.1 Phase 2 Studies

5.3.1.1 Rolando, 1994

In this randomized, controlled, observer-masked, parallel-group study, 100 subjects aged ≥ 18 years with dry eye due to primary KCS or Sjögren's syndrome were randomly assigned 1:1 to receive 1 drop of SH ophthalmic solution 0.18% or HPMC/Dextran 70 solution in each eye 6 times daily for 60 days (4). The objectives of the study were to compare the effect of SH ophthalmic solution 0.18% and HPMC/Dextran 70 eye drops on tear volume and tear stability, to evaluate the subsequent effect on tear mucus ferning and on the condition of ocular surface cells, and to assess the tolerability of the 2 drugs.

The following efficacy measures were evaluated at Days 15, 30, and 60: objective--Schirmer's I test, TBUT, Rose Bengal and fluorescein staining of the cornea and conjunctiva, tear mucus ferning pattern, impression cytology, presence of filamentous secretion; and subjective--classification of symptom intensity (burning, photophobia, foreign-body sensation, and pain) and investigator assessment of outcome and therapeutic efficacy.

Significant treatment differences in favor of SH ophthalmic solution 0.18% were reported at all time points for mean Schirmer's I test values (SH ophthalmic solution 0.18%, 11.45 mm versus HPMC, 7.64; $P = 0.0001$), mean TBUT values (SH ophthalmic solution 0.18%, 10.68 seconds versus HPMC, 8.37 seconds; $P = 0.0001$), mean Rose Bengal staining scores (SH ophthalmic solution 0.18%, 0.41 versus HPMC, 1.23; $P = 0.0001$) and mean fluorescein staining scores (SH ophthalmic solution 0.18%, 0.34 versus HPMC, 1.22; $P = 0.0001$), and for symptoms of burning and foreign-body sensation (all $P < 0.05$). The severity of photophobia and pain was significantly decreased on Days 30 and 60 for SH ophthalmic solution 0.18% versus HPMC ($P = 0.0001$). A treatment benefit was also shown for SH ophthalmic solution 0.18% at Day 60 for impression cytology, tear mucus ferning, and investigator efficacy assessment (all $P < 0.05$). The investigator's conclusion was that SH ophthalmic solution 0.18% eye drops are an effective treatment for the signs and symptoms of moderate and severe dry eye due to primary KCS and Sjögren's syndrome.

5.3.1.2 Rapisarda, 1994

In a nearly identical randomized, controlled, observer-masked, parallel-group study, 120 subjects (age range, 26–78 years) with dry eye from primary KCS or Sjögren's syndrome were randomly assigned 1:1 to receive 1 drop of SH ophthalmic solution 0.18% or HPMC/Dextran 70 solution in each eye, 6 times daily for 60 days (**3**). The objectives of the study were to compare the effect of SH ophthalmic solution 0.18% versus HPMC/Dextran 70 eye drops on tear volume and tear stability, to evaluate their effect on the osmolarity of the tear film, and to assess the tolerability of the 2 drugs. The following efficacy measures were evaluated at Days 15, 30, and 60: objective--Schirmer's I test, TBUT, Rose Bengal and fluorescein staining of the cornea and conjunctiva, tear osmolarity, presence of filamentous secretion; and subjective--classification of symptom intensity (burning, photophobia, foreign-body sensation, and pain) and investigator assessment of outcome and therapeutic efficacy.

Significant treatment differences were reported for SH ophthalmic solution 0.18% versus HPMC at Day 60 in the mean Schirmer's I test values (SH ophthalmic solution 0.18%, 10.04 mm versus HPMC, 6.24 mm; $P = 0.0001$); mean TBUT values (SH ophthalmic solution 0.18%, 7 seconds versus HPMC, 4.81 seconds; $P = 0.0001$); mean Rose Bengal staining scores (SH ophthalmic solution 0.18%, 0.34 versus HPMC 1.62; $P = 0.0001$) and mean fluorescein staining scores (SH ophthalmic solution 0.18%, 0.38 versus HPMC, 1.36; $P = 0.0001$) scores; and for the symptoms of burning, foreign-body sensation, and photophobia (all $P \leq 0.05$). A treatment benefit of SH ophthalmic solution 0.18% was also shown at Day 60 for tear osmolarity and investigator efficacy assessment (all $P < 0.05$). The investigator concluded that SH ophthalmic solution 0.18% eye drops are an effective

treatment for the signs and symptoms of moderate and severe dry eye resulting from primary KCS and Sjögren's syndrome.

5.3.1.3 Baudouin, 2001

In this single-center, randomized, masked-assessor, controlled, parallel-group, Phase 2 study, 22 subjects with moderate dry eye (KCS) and superficial keratitis due to Sjögren's syndrome, or diagnosed as primary dry eye, were treated with 1 drop of SH ophthalmic solution 0.18% or Celluvisc® in each eye 3 times per day or as needed for 56 days (**5**). Objective efficacy measures included tear prism height, corneal topography, Schirmer's I test, corneal staining with fluorescein, staining with lissamine green, TBUT, and flow cytometry in impression cytology. Subjective efficacy measures consisted of symptom intensity on VAS, impact of symptoms on daily life (0–3 scale), and comfort of the drops (0–2 scale). Safety assessments included BCVA, slit lamp examination, AE reporting, and examination of ocular adnexa.

Fluorescein staining scores (type, extent, and depth) decreased more rapidly in subjects treated with SH ophthalmic solution 0.18% than in those treated with Celluvisc®. Decreases in corneal and nasal conjunctival lissamine green staining scores were observed in both treatment groups. Temporal staining tended to stabilize in the SH ophthalmic solution 0.18% group, whereas it decreased in the Celluvisc® group. In the SH ophthalmic solution 0.18% group, total lissamine green staining scores progressively decreased at Days 7 and 28 and stabilized at Day 56. In the Celluvisc® group, values decreased quickly at Day 7, but tended to increase from Day 28 to Day 56. Slit lamp examination results showed improvement in subjects treated with SH ophthalmic solution 0.18%. Tear prism height values increased slightly in both groups, but no significant between-group differences were observed. At Day 56, mean values for corneal topography increased in the SH ophthalmic solution 0.18% group and decreased in the Celluvisc® group. There was a trend towards an increase in the mean TBUT value in both groups. Regarding flow cytometry, there was a significant ($P = 0.031$) reduction in CD44 expression in the SH ophthalmic solution 0.18% group. Compared with baseline values, both groups showed a strong tendency towards a decrease in the percentage of HLA-DR positive cells and an increase in the mucus cells expressing CD63 and UIC2 (see Section 4.3).

The conclusion of the study was that SH ophthalmic solution 0.18% was a better treatment than Celluvisc® in subjects with KCS and superficial keratitis due to Sjögren's syndrome or diagnosed as primary dry eye.

5.3.2 Phase 4 Studies

5.3.2.1 Prabhasawat, 2007

This Phase 4 study assessed the short-term efficacy of SH ophthalmic solution 0.18% in subjects with evaporative tear-sufficient dry eye due to lipid tear deficiency (**10**). In this study, 10 subjects were treated with 1 drop of SH ophthalmic solution 0.18% in 1 eye and 1 drop of isotonic HPMC 0.3%/Dextran 0.1% in the other eye. Clinical assessments of each eye included the intensity of 5 dry eye symptoms (soreness, scratchiness, dryness, grittiness, and burning) using the VAS; visual acuity; external and slit-lamp examination on lid, lashes, and meibomian glands; staining with fluorescein and Rose Bengal; NIBUT; TBUT; and tear volume (Schirmer's I test). Symptoms and NIBUT were assessed at 15, 30, 60, and 90 minutes after instillation. Any AEs were reported throughout the study to assess safety.

Both products showed a statistically significant improvement ($P < 0.05$) for both treatment groups in NIBUT at 15, 30, and 60 minutes compared with baseline. However, the subjects treated with SH ophthalmic solution 0.18% showed greater improvement at all time points and a longer duration (> 90 minutes) than the subjects treated with HPMC 0.3%/Dextran 0.1% (60 minutes). Differences were statistically significant at 30 minutes ($P = 0.04$) and at 60 minutes ($P = 0.005$) for SH ophthalmic solution 0.18%. There was no significant difference between the 2 treatment groups for the VAS assessment, although the subjects experienced relief of their symptoms.

Overall, SH ophthalmic solution 0.18% and HPMC 0.3%/Dextran 0.1% showed a statistically significant improvement ($P < 0.05$) in NIBUT, but the group treated with SH ophthalmic solution 0.18% showed a statistically significantly ($P < 0.05$) greater improvement and a longer duration in NIBUT than the group treated with HPMC 0.3%/Dextran 0.1%.

5.3.2.2 Johnson, 2008

This randomized, double-masked, Phase 4 study compared the efficacy of eye drops containing carbomer 934 0.3% or SH ophthalmic solution 0.18% in treating moderate dry eye (**6**). A total of 65 subjects with moderate dry eye were randomly assigned to 2 groups (carbomer 934 0.3% [n = 33] or SH ophthalmic solution 0.18% [n = 32]). Subjects were instructed to instill the drops 2 to 8 times per day for 28 days. The primary endpoints measured were tear film break-up time with fluorescein (TBUT) and without fluorescein (NIBUT), corneal fluorescein staining, conjunctival lissamine green staining, and the severity of the symptoms of ocular irritation, as assessed by the ocular comfort index (OCI). The OCI questionnaire consists of 6-question doublets that rate the frequency and intensity of dryness, grittiness, stinging, pain, and itching of the eyes within the last week using a 7-category (0–6) rating scale.

Rather than summing these ratings to arrive at an ordinal ranking, OCI uses a variant of item response theory known as Rasch analysis in which the raw data counts are transformed into estimates of a person's "ability" on a linear interval scale. This linear interval scale is better able to quantify change. The scoring technique is based on probability and uses statistical methods to account for missing data more satisfactorily than traditionally scored questionnaires. In addition, at the end of the study, subjects were asked (1) the average number of times per day they instilled the product and (2) the duration of any blurring after instillation of the product.

Eye drops with either carbomer or SH ophthalmic solution 0.18% showed a similar reduction in the extent of ocular surface staining and the severity of symptoms in subjects with moderate dry eye. The eye drops containing SH ophthalmic solution 0.18% reduced corneal and conjunctival staining more than the eye drops with carbomer. The difference between the 2 treatment groups for corneal staining was 0.22 log units ($P = 0.036$), and the difference between the 2 treatment groups for lissamine green staining was 0.76 log units ($P = 0.012$). A clinically significant change was defined as 0.5 log units. The values for TBUT and NIBUT did not show a statistically significant change from baseline for either product. There was an improvement in OCI scores for both treatment groups. Sodium hyaluronate ophthalmic solution 0.18% improved from -4.8 to -8.7 units ($P < 0.01$), and carbomer improved from -5.1 to -8.5 units ($P < 0.01$). A negative number indicates a reduction in the severity of symptoms from baseline after treatment. The difference in effect between the 2 groups was -2.6 to 2.4 units, with a clinically significant change defined as 3 units. The mean number of drops per day was 2 drops for both products. More subjects experienced visual disturbance on instillation of 1 minute or longer with the eye drops containing carbomer (48% [16/33]) than with the eye drops containing SH ophthalmic solution 0.18% (6% [2/32]).

In conclusion, both of the eye drops evaluated were effective for the treatment of moderate dry eye, but the eye drops with SH ophthalmic solution 0.18% had the benefit of therapeutic efficacy as well as less frequent occurrence of visual disturbance.

5.4 Maintenance of Long-Term Benefit

In the studies conducted by Rolando (**4**) and Rapisarda (**3**), SH ophthalmic solution 0.18% was shown to be effective through 2 months (60 days) of continuous dosing in both eyes, 6 times per day (see Sections 5.3.1.1 and 5.3.1.2, respectively, for summaries). Long-term studies beyond 60 days have not been conducted.

5.5 Efficacy Conclusions

Sodium hyaluronate ophthalmic solution 0.18% is a marketed product with a well-established profile of efficacy for the treatment of the signs and symptoms of dry eye disease, as demonstrated by clinical studies and post-marketing reports.

Ten clinical studies assessed the efficacy of SH ophthalmic solution 0.18% in 512 subjects who were treated with the product for up to 2 months. Seven studies were randomized and controlled and 3 were uncontrolled and exploratory. The results from individual studies showed statistically significant benefits of the product when compared with a placebo or active control in the following signs: lissamine green staining, corneal staining (fluorescein and Rose Bengal), Schirmer's I test, TBUT, and impression cytology. The studies support the efficacy of the product and further demonstrate the uniqueness of the SH formulation in its ability to increase the number of goblet cells (which stimulate mucus production) and decrease tear osmolarity to normal physiological levels. Furthermore, in clinical dose-finding studies, the product has demonstrated TBUT values that were increased for up to 4 hours after instillation (Hamano, 1993; Hamano, 1996; Sand, 1989). The tear film was significantly more uniform after instillation, which had a positive effect on visual acuity.

The results from the clinical studies conducted with the product, in which the efficacy results of the two Phase 3 studies (**1**, **2**) meeting the regulatory standard of substantial evidence of safety and efficacy were presented in detail, are compelling evidence of the safety and efficacy of the product. The results from the Baudouin 2005 (**2**) and RP-001 (**1**) studies showed that for most objective and subjective outcomes assessed, SH ophthalmic solution 0.18% was more effective than control (saline in the Baudouin 2005 study and vehicle in Study RP-001) in relieving the signs and symptoms of dry eye, with an early onset of action observed at 7 days. Results from the Baudouin 2005 study showed that SH ophthalmic solution 0.18% was significantly more effective than saline in reducing the following objective and subjective measures of dry eye: corneal fluorescein staining at Day 28, lissamine green staining at Days 7 and 28, and global symptom frequency at Days 7 and 28. Results from Study RP-001 showed a statistically significant benefit for SH ophthalmic solution 0.18% over vehicle in improving lissamine green staining scores at Days 7 and 14 and in improving global symptom frequency scores, summed VAS symptom scores, and composite symptom intensity and symptom frequency scores at Day 7.

Of interest is the strength of the evidence of efficacy at Day 7, (Table 8 and Table 9). Baudouin (2005) studied the treatment effects at Days 7 and 28. The Day 7 primary endpoint was selected in Study RP-001 to confirm the findings observed at Day 7 in the Baudouin 2005 study. This goal was achieved in Study RP-001, and indicates that use of SH

ophthalmic solution 0.18% will result in rapid clinical improvement and relief of symptoms in patients with dry eye disease.

Comparison with the vehicle as a control has proven to be a significant hurdle for many product candidates for the treatment of the signs and symptoms of dry eye disease. The superiority of this formulation of SH ophthalmic solution 0.18% has been demonstrated in the same sign and the same symptom when compared with a saline placebo in the Baudouin 2005 study and compared with a vehicle placebo in Study RP-001. This is compelling and scientifically thorough evidence of the efficacy of the product in patients with dry eye disease. These findings represent the first dry eye drug candidate to demonstrate superiority to both saline and vehicle on the same sign and the same symptom in two separate clinical trials, meeting the regulatory standard of substantial evidence of safety and efficacy.

Further, since the safety of SH is widely established in these studies and elsewhere (see Section 6), the benefit-to-risk evaluation is overwhelmingly positive. The substantive efficacy and safety findings provide the pivotal support for regulatory approval of SH ophthalmic solution 0.18% for the treatment of the signs and symptoms of dry eye disease.

6. Clinical Safety

6.1 Safety Evaluation Plan

Seven of the 10 clinical studies reported in the efficacy portion of this document (**1**, **2**, **3**, **4**, **5**, **7**, **10**) also assessed the safety of the product in a total of 435 subjects who were treated for up to 2 months. Three of these studies form the basis of the safety profile that will be reflected in the labeling: one Phase 2 study (**5**) and two Phase 3 studies (**1**, **2**). The total number of subjects in the safety population for these three studies was 305. The remaining four studies will not be discussed in detail because the veracity of the data captured in those studies are not verifiable as compliant with Good Clinical Practice or the International Conference on Harmonisation (**3**, **4**, **7**, **10**). In these four studies, 130 subjects were exposed to the product and no AEs were reported.

The three clinical studies supporting the proposed labeling were randomized and controlled studies conducted in subjects with dry eye. The Baudouin 2005 study and Study RP-001 were multicenter and double-masked, and the Baudouin 2001 study was conducted at a single center and investigator-assessed. The Baudouin 2001 and Baudouin 2005 studies were conducted in France by TRB Chemedica, the sponsor of SH ophthalmic solution 0.18% in Europe. These two studies compared the product to Celluvisc® (sodium CLV 1% eye drops) or to saline 0.9%, respectively. Study RP-001 was conducted in the US by River Plate Biotechnology, Inc. to compare SH ophthalmic solution 0.18% to its vehicle. The Baudouin

2001 study evaluated safety related to treatment with 1 drop/day of the product or Celluvisc® administered 3 times per day or as needed for 56 days, while the Baudouin 2005 study evaluated the safety of 1 drop of the product or saline administered at least 3 and up to 8 times per day or as needed for 28 days. Study RP-001 evaluated the product at a dose of 1 to 2 drops instilled into each eye at least 3 times per day and up to 6 times per day for 14 days. Safety measurements evaluated in these studies included slit lamp examination, BCVA, ophthalmic examination, and collection of AEs. In addition, Study RP-001 assessed IOP.

6.2 Extent of Exposure

Overall, a total of 305 subjects in the three studies (Baudouin 2001: N = 10; Baudouin 2005: N = 74; and Study RP-001: N = 221) were exposed to at least 1 drop per day of the product, ranging from 1 day to 60 days (safety population), as defined in the individual study protocols. In these three studies, the total number of subjects randomized to receive study drug was 306; however, 1 subject did not receive study drug after randomization, and therefore, by definition, this subject was not included in the safety population.

In the Baudouin 2001 study, subjects received the study drug or active control (Celluvisc®); the mean duration of exposure was 56 days in each treatment group. Subjects in the Baudouin 2005 study were exposed to the study drug or placebo (saline 0.9%) for a mean duration of 28 days. In Study RP-001, subjects were exposed to the study drug or placebo (vehicle) for a mean duration of 15.2 ± 1.82 days and 14.8 ± 1.67 days, respectively.

The mean number of daily instillations of the product was 3.7 and 3.8 in the Baudouin 2005 and RP-001 studies, respectively. In Baudouin 2005, the average number of daily instillations was estimated by subject-reported usage captured on diary cards and accountability of study drug. In Study RP-001, the average number of daily instillations was estimated by accountability of the study drug.

An estimate of the number of post-marketing patients treated has been calculated from the total sales volume since the product was launched in January 1998 until December 31, 2008. During this time period, 9,488,689 boxes (of 20 monodose units) of Vismed®, Vislube®, and Hylovis® were sold worldwide. It was assumed that each patient used at least 3 boxes and up to 36 boxes of 20 monodoses per year (gross estimation). Using these assumptions, an estimated 263,575 to 3.2 million patients have been exposed to the product since it was launched.

6.3 Summary of Adverse Events

Treatment-emergent adverse events (TEAEs) were summarized by system organ class and preferred term using the Medical Dictionary of Regulatory Activities (MedDRA)

Version 10.0. For the two studies conducted in France (2, 5), AE data were updated to MedDRA Version 10.0 to be consistent with Study RP-001 and were subsequently integrated with data from Study RP-001. All AE data are based on the safety population, defined as any subject who received at least 1 dose of study drug.

Of the 305 subjects who were treated with SH ophthalmic solution 0.18% in the three clinical studies contributing to the safety database, 14.4% (44/305) reported at least 1 AE, and only 1 subject (0.3% [1/305]) experienced a SAE, which was considered to be unrelated to the product. Overall, 3 subjects (1% [3/305]) treated with SH ophthalmic solution 0.18% withdrew due to AEs (Table 10). The total number of subjects included in the safety database includes those in Baudouin 2001 (N = 10), in which no AEs were reported. Accordingly, the TEAEs in Table 10 are shown for the other two studies, Baudouin 2005 and RP-001.

Table 10 Comparison and Integrated Analysis of Treatment-Emergent Adverse Events (Safety Population)

Adverse Event Categories	Baudouin 2005		Study RP-001		Total Studies
	SH Ophthalmic Solution 0.18% (N=74)	Saline (N=77)	SH Ophthalmic Solution 0.18% (N=221)	Vehicle (N=222)	SH Ophthalmic Solution 0.18% (N=305[a])
No. (%) of subjects reporting any AEs	10 (13.5%)	9 (11.7%)	57 (25.8%)	48 (21.6%)	67 (22.0%)
No. of AEs reported	11	9	94	74	105
No. (%) of subjects reporting					
0 AEs	64 (86.5%)	68 (88.3%)	164 (74.2%)	174 (78.4%)	238 (78.0%)
1 AE	9 (12.2%)	9 (11.7%)	35 (15.8%)	33 (14.9%)	44 (14.4%)
> 1 AEs	1 (1.4%)	0	22 (10.0%)	15 (6.8%)	23 (7.5%)
No. (%) of subjects reporting AEs by maximum intensity					
Mild	5 (6.8%)	6 (7.8%)	42 (19.0%)	34 (15.3%)	47 (15.4%)
Moderate	5 (6.8%)	3 (3.9%)	13 (5.9%)	10 (4.5%)	18 (5.9%)
Severe	0	0	2 (0.9%)	4 (1.8%)	2 (0.7%)
No. (%) of subjects reporting AEs by relationship to study drug					
Not related	9 (12.2%)	5 (6.5%)	10 (4.5%)	8 (3.6%)	19 (6.2%)
Unlikely related	0	1 (1.3%)	13 (5.9%)	12 (5.4%)	13 (4.3%)
Possibly related	1 (1.4%)	2 (2.6%)	32 (14.5%)	28 (12.6%)	33 (10.8%)
Related	0	1 (1.3%)	2 (0.9%)	0	2 (0.7%)
No. (%) of subjects reporting any AEs leading to withdrawal	1 (1.4%)	2 (2.6%)	2 (0.9%)	1 (0.5%)	3 (1.0%)
No. (%) of subjects reporting any AEs leading to interruption of study medication	0	0	0	0	0
No. of subjects reporting any SAEs	0	0	1 (0.5%)	1 (0.5%)	1 (0.3%)
No. (%) of deaths	0	0	0	0	0

Abbreviations: AE = Adverse event; N = Number of subjects in the safety population; SAE = Serious adverse event; SH = Sodium hyaluronate.

a. Includes Baudouin 2001, in which no AEs were reported (N = 10 in active treatment group).

6.3.1 Treatment-Emergent Adverse Events

6.3.1.1 Ocular Treatment-Emergent Adverse Events

Because SH ophthalmic solution 0.18% is delivered by topical instillation into the eyes, ocular TEAEs are of greatest clinical relevance. Across studies, the ocular TEAEs occurring in ≥ 1% of subjects treated with SH ophthalmic solution 0.18% were dry eye (5.9% [18/305]), eye pain (4.3% [13/305]), eye irritation (2.0% [6/305]), foreign-body sensation (1.6% [5/305]), reduced visual acuity (1.3% [4/305]), eye pruritis (1.3% [4/305]), blurred vision (1.3% [4/305]), ocular hyperaemia (1.0% [3/305]), and eyelid margin crusting (1.0% [3/305]; Table 11). None of these TEAEs occurred at a frequency > 3% higher in subjects treated with SH ophthalmic solution 0.18% compared with control treatment.

Of these events, the majority were mild (dry eye [5.6% (17/305)], eye pain [2.6% (8/305)], eye irritation [2.0% (6/305)], foreign-body sensation [1.3% (4/305)], reduced visual acuity [1.3% (4/305)], eye pruritis [0.7% (2/305)], blurred vision [1.3% (4/305)], ocular hyperaemia [0.7% (2/305)], and eyelid margin crusting [1.0% (3/305)]; data not shown).

In addition, few ocular TEAEs were considered related to study drug (eye pain [0.3% (1/305)], eye pruritis (0.3% [1/305]), and blurred vision (0.3% [1/305]); data not shown).

Table 11 Summary of Ocular Treatment-Emergent Adverse Events Occurring in ≥1% of Subjects Across Studies: Incidence Without Regard to Intensity or Relationship to Study Drug by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Baudouin 2005		Study RP-001		Total Subjects SH Ophthalmic Solution 0.18% (N=305[a])
	SH Ophthalmic Solution 0.18% (N=74)	Saline (N=77)	SH Ophthalmic Solution 0.18% (N=221)	Vehicle (N=222)	
Eye Disorders, n (%)					
Dry eye	0	0	18 (8.1%)	14 (6.3%)	18 (5.9%)
Eye pain	0	0	13 (5.9%)	7 (3.2%)	13 (4.3%)
Eye irritation	2 (2.7%)	0	4 (1.8%)	5 (2.3%)	6 (2.0%)
Foreign-body sensation in eyes	0	0	5 (2.3%)	7 (3.2%)	5 (1.6%)
Visual acuity reduced	0	0	4 (1.8%)	6 (2.7%)	4 (1.3%)
Eye pruritis	0	0	4 (1.8%)	4 (1.8%)	4 (1.3%)
Vision blurred	0	0	4 (1.8%)	0	4 (1.3%)
Ocular hyperaemia	0	0	3 (1.4%)	3 (1.4%)	3 (1.0%)
Eyelid margin crusting	0	0	3 (1.4%)	1 (0.5%)	3 (1.0%)

Abbreviations: N = Number of subjects in the safety population; SH = Sodium hyaluronate.
a. Includes Baudouin, 2001, in which no AEs were reported (N=10 in the active treatment group).

6.3.1.2 Non-Ocular Treatment-Emergent Adverse Events

Across studies, the systemic, nonocular TEAEs with the highest incidence in subjects treated with the study drug were upper respiratory tract infection (0.7% [2/305]); arthritis (0.7% [2/305]); headache (0.7% [2/305]), migraine (0.7% [2/305]), and depression (0.7% [2/305]). The majority of these events were mild to moderate and judged to be unrelated to study drug. One subject in Study RP-001 had a severe headache that was considered possibly related to study drug (data not shown).

6.4 Deaths, Serious Adverse Events, and Withdrawals Due to Adverse Events

6.4.1 Deaths

No deaths occurred in any of the studies.

6.4.2 Serious Adverse Events

The overall incidence of SAEs in the three clinical studies was very low, with SAEs reported for 1 of 305 subjects (0.3%) exposed to the study drug and 1 of 299 subjects (0.3%) exposed to placebo. In Study RP-001, 1 of 221 subjects (0.5%) treated with the study drug experienced 1 SAE (79-year-old female; viral gastroenteritis) and 1 of 222 subjects (0.5%) in the vehicle group had 1 SAE (82-year-old male; benign mass in colon). Both events were non-ocular and considered to be unrelated to study drug.

No SAEs were reported in the Baudouin 2001 and Baudouin 2005 studies.

6.4.3 Withdrawals Due to Adverse Events

Withdrawals due to AEs were rare. Only 1% of the total population across studies withdrew from the study due to an AE (3/305) in the study drug treatment groups (1 subject in the Baudouin 2005 study and 2 subjects in Study RP-001). Similarly, 1% of the total population withdrew from the study due to an AE (3/299) in the control groups (2 subjects in the Baudouin 2005 study and 1 subject in Study RP-001).

In Study RP-001, 1 subject in the active group withdrew due to mild blurred vision, which was considered possibly related to study drug. The second subject in the active group withdrew due to moderate viral conjunctivitis and moderate ocular hyperemia (both considered to be unrelated to study drug) and severe headache (considered to be possibly related to study drug).

In the Baudouin 2005 study, 1 subject in the active group withdrew due to mild eye irritation, “burning after instillation,” which was considered to be possibly related to study drug.

No withdrawals due to AEs were reported in the Baudouin 2001 study.

6.5 Other Ocular Safety Assessments

Evaluations of ocular health and function were performed to monitor the safety of the product during clinical studies.

6.5.1 Slit Lamp Examination

In the Baudouin 2001 study, a trend toward improvement in limbal hyperemia and bulbar conjunctival hyperemia was observed in the active group versus the control group at each study visit. The worsening observed in some subjects was attributable to the normal evolution of the pathology. In the Baudouin 2005 study, there was a trend for mean slit-lamp values to decrease in both the active and control groups. No worsening of signs related to the study drug was observed in any of the subjects. In Study RP-001, no clinically significant differences were observed between the active and control groups for change from baseline in slit lamp examination.

6.5.2 Best-Corrected Visual Acuity

In the Baudouin 2001 study, no significant difference was observed in BCVA values between the active and control groups at baseline and at the last treatment visit (Day 56). In the Baudouin 2005 study, 3 subjects in the active group had a decrease of ≥ 2 lines compared with 1 subject in the control group at the last treatment visit (Day 28). In Study RP-001, no subjects in either treatment group had a decrease of ≥ 2 lines at the last treatment visit (Day 14).

6.5.3 Intraocular Pressure

In Study RP-001, differences between the active and control groups for change from baseline in IOP were unremarkable. Intraocular pressure was not assessed in the Baudouin 2001 and Baudouin 2005 studies.

6.5.4 Dilated Fundus Examination Scores

In Study RP-001, no clinically significant differences were observed between the active and control groups in changes from baseline for the dilated fundus examination scores. This parameter was not assessed in the Baudouin 2001 and Baudouin 2005 studies.

6.5.5 Examination of Ocular Adnexa

In the Baudouin 2001 study at baseline, 3 of 10 subjects in the active group and 2 of 11 subjects in the control group had blepharitis. No significant differences were observed

between the 2 treatment groups at baseline for this parameter. This examination was not conducted in the Baudouin 2005 and RP-001 studies.

6.5.6 General External Ophthalmic Examination

In the Baudouin 2005 study at baseline, the majority of subjects in both the active and control groups had no findings on the eyelids (89% and 93.5%, respectively) and periocular area (98.6% and 100%, respectively). There were no significant changes in either treatment group throughout the study. This examination was not conducted in the Baudouin 2001 study and Study RP-001.

6.6 Long-Term Safety Data

Long-term safety (beyond 60 days) was not assessed in these clinical studies.

6.7 Comparison of Adverse Event Profile with Other Drugs in the Class

The AE profile of SH ophthalmic solution 0.18% was consistent with that found with other topical SH ophthalmic solutions. Four controlled clinical studies were conducted with SH solutions other than the proprietary formulation described in the NDA. Condon, et al (Condon, 1999) evaluated the safety and efficacy of SH 0.1% compared with saline in the treatment of symptoms of severe dry eye in a multicenter, double-masked, crossover study. Eighty-four subjects received 1 to 2 drops of SH 0.1% or saline 3 to 4 times per day. After 28 days, the subjects crossed over to take the comparator for another 28 days. No AEs were reported for any of the subjects who instilled SH.

In a multicenter, randomized, double-masked study comparing the efficacy of two ophthalmic solutions containing hyaluronic acid, but of different osmolarities (hypotonic and isotonic), 23 AEs were classified as related to the study treatment (blepharitis or allergic reactions) with no between-group differences (Papa, 2001). Two treatment-related AEs were described as severe (local allergic reaction) and required corticosteroids. Two SAEs required the subjects to be hospitalized and were classified as not treatment-related.

In a multicenter, randomized, double-masked study, 104 subjects with dry eye were treated with SH 0.1% or vehicle 6 times per day (Shimmura, 1995). Two subjects developed signs of allergic conjunctivitis; 1 subject had to withdraw due to worsening of symptoms.

No treatment-related AEs occurred in a multicenter, randomized, double-masked study exploring the long-term (3 months) effect of 1 drop 4 to 8 times per day of SH 0.15% versus saline on the ocular surface of subjects with moderate to severe dry eye (Aragona, 2002).

6.8 Worldwide Marketing Experience

Sodium hyaluronate ophthalmic solution 0.18%, marketed as Vismed®, Vislube®, and Hylovis®, is approved as a Class IIb medical device in 41 countries and as a drug in 2 countries, and has been on the market in Europe, Australia, and parts of Asia since January 1998. In all countries where Vismed®, Vislube®, and Hylovis® are registered, except France and the United Kingdom, it is intended to be used for the alleviation of the sensation of dryness and other minor complaints of no pathological significance, as well as burning and ocular fatigue induced (eg, by dust, smoke, dry heat, air conditioning, extended computer screen use, or contact lens wear). In France and the United Kingdom, the product is intended to be used for moderate or severe sensations of dryness in the eye (as approved by the German Notified Body TÜV). Vislube® brand product is more specifically intended to be used for the alleviation of the sensation of dryness, discomfort, or distorted vision during contact lens wear.

Based on sales figures from territories in which this proprietary formulation of SH ophthalmic solution 0.18% is marketed, at least 263,575 patients and as many as 3.2 million patients have been exposed to the product since it was launched in January 1998. From that time through December 31, 2008, only 39 medical complaints have been reported (Table 12). The majority of complaints filed are "burning sensation" and "hypersensitivity or intolerance," which are interpreted to be "minor" in nature. None of the reported complaints required changes to the product safety labeling.

Table 12 Spontaneous Complaint Reports (Vismed® and Vislube® Brands of Sodium Hyaluronate Ophthalmic Solution 0.18%)

Adverse Event	Total Number of Complaints, n
Burning sensation	16
Hypersensitivity/intolerance	13
Eye reddening	5
Foreign-body sensation	1
Eye injury [a]	1
Local swelling	1
Blurred vision	1
Other	1
Total	**39**

a. This complaint was due to incorrect handling of the delivery device.

Of the comfort-related events reported, none were classified as "allergic reactions" and the patients were not tested for allergy to the SH ophthalmic solution 0.18%.

Several cases of severe synovitis have been reported in the literature regarding the administration of preparations of SH solution injected into synovial joint spaces as treatment for arthritis and degenerative joint disease. Follow-up investigations of intra-articular hyaluronate products were conducted to determine the cause of these induced reactions. In rare instances, responses were induced using a cross-linked compound containing not only the bacteria-derived SH that is the active ingredient in the SH ophthalmic solution 0.18%, but also a hyaluronate produced from cocks combs, thus containing avian proteins. Results for cross-linked hyaluronate were compared with those for endogenous hyaluronate. They showed that, in guinea pigs, a specific immunologic response was elicited by the cross-linked products (Goomer, 2005), but not with native hyaluronate. The explanatory hypothesis is that the cross-linking of hyaluronate with formaldehyde would produce an immunogenic protein (Hamburger, 2005). Additionally, immunogenicity tests performed in rabbits showed no production of hyaluronic acid-specific antibodies (Bucher, 2002).

Because the sodium hyaluronate in the SH ophthalmic solution 0.18% is obtained by fermentation from bacteria, it is devoid of animal protein. Therefore, there is currently no evidence of the SH ophthalmic solution 0.18% triggering an allergic reaction.

6.9 Safety Conclusions

Sodium hyaluronate ophthalmic solution 0.18%, known alternatively by trade names Vismed®, Vislube®, and Hylovis®, is a marketed product with a well-established safety profile. Clinical studies and post-marketing reports demonstrate that the product is well tolerated for the treatment of the signs and symptoms of dry eye disease.

Three randomized and controlled studies conducted with the product form the basis of the safety profile reflected in the proposed labeling: one Phase 2 study (**5**) and two Phase 3 studies (**1**, **2**). The results of these studies show that the safety profile of the drug product is excellent, with a very low incidence of AEs. Of the 305 subjects who were treated with the product in the 3 studies, only 67 (22.0%) experienced 1 or more AEs (1 AE reported, n = 44; > 1 AE reported, n = 23) and only 1 subject experienced an SAE, which was considered to be unrelated to the product. Across the three studies, 3 subjects treated with the product withdrew due to AEs, all of which were judged to be unrelated or possibly related to study drug.

Because the product is an ophthalmic solution delivered by topical instillation, ocular AEs are of greatest clinical relevance. Across studies, the ocular AEs with the highest incidence in subjects treated with the product were dry eye, eye pain, eye irritation, foreign-body sensation, reduced visual acuity, eye pruritis, blurred vision, ocular hyperaemia, and eyelid margin crusting. Of these events, most were mild and few were judged to be related to the

study drug. Only 2 subjects in the active groups and 1 subject in the vehicle groups reported AEs that were considered to be related to the study drug.

The product has been on the market in Europe, Australia, and parts of Asia since January 1998. It is approved as a Class IIb medical device in 41 countries and as a drug in 2 countries. Approximately 9.5 million product units were sold during the period between launch in January 1998 and December 31, 2008. An estimated 232,000 to 2.8 million patients have been exposed to the product since it was launched, and there were only 39 reports of medical complaints related to the product. None of the reported events required changes to the product safety labeling. Additionally, more than 20 products containing SH are currently marketed in the US. These SH-containing products are used across multiple therapeutic areas via multiple routes of administration and have demonstrated favorable safety profiles in a variety of patient populations.

Overall, the clinical safety data for SH ophthalmic solution 0.18% presented in this summary show that the product is safe and well tolerated. During more than 10 years of research and marketing activities, very few AEs have been documented in either clinical studies or post-marketing reports of the product. Based on this evidence, and the favorable results from the nonclinical studies, SH ophthalmic solution 0.18% has an excellent safety profile.

7. Benefit/Risk Analysis

Sodium hyaluronate ophthalmic solution 0.18% is a patented eye drop formulation for which clinical study results demonstrate efficacy in both signs and symptoms of dry eye disease, with a good safety and tolerability profile. The benefit to risk ratio of this drug candidate is very positive as substantiated by a favorable onset of relief of the signs and symptoms of dry eye disease in patients within 7 days and a well-established safety profile.

Sodium hyaluronate was chosen as the active ingredient in the drug product because of its unique viscoelastic properties which allow it to behave differently during and between blinks (Bron, 1985; Tiffany, 1994). During blinks, shear stress causes the molecules of SH to align with each other. As a result, the solution becomes elastic and relatively nonviscous and spreads easily over the surface of the cornea. Between blinks, the molecules of SH form a tangled meshwork, and the solution becomes less elastic and more viscous. This mechanism stabilizes the precorneal tear film and maximizes the residence time of the solution on the surface, enabling it to protect and lubricate the ocular surface. Protection of the ocular surface is particularly important in the treatment of dry eye disease. This characteristic of the molecule has led to SH being approved for use in ocular surgeries, such as cataract surgery, where it is used to protect the endothelium from the surgical instrument, and stands up to mechanical shearing forces because it does not break up and remains on the endothelium. Sodium hyaluronate is also used in other ocular surgeries as a masking agent.

The results of two randomized, Phase 3 clinical studies conducted with SH ophthalmic solution 0.18% show significant benefit in both an objective sign (lissamine green staining) and a subjective symptom (global symptom frequency) and meet the regulatory standard of substantial evidence of safety and efficacy. These results are notable in that numerous clinical studies with other products have been unable to replicate successful treatment of both an objective sign and a subjective symptom in subjects with dry eye disease. The benefits in corneal erosion and relief from symptoms with SH ophthalmic solution 0.18% are apparent after 1 week of treatment. Symptom intensity scores, the composite index of symptom intensity and symptom frequency, and a trend in the global impact of dry eye scores on the daily life questionnaire are supportive of these findings.

In a side-by-side comparison of the two Phase 3 clinical studies (**1**, **2**), SH ophthalmic solution 0.18% administered 3 to 6 times daily was significantly more effective than placebo (either saline or vehicle) when administered over a 14-day or 28-day treatment period. The lissamine green staining score, a sensitive indicator of the health of the cornea, was significantly lower on Day 7 in both studies in subjects treated with SH ophthalmic solution 0.18% compared to subjects treated with placebo. It is important to note that global symptom frequency scores at Day 7 were also significantly lower in subjects treated with active drug

versus placebo, indicating that subjects were not experiencing dry eye symptoms as frequently as they had at baseline.

The product, known alternatively by the trade names Vismed®, Vislube®, and Hylovis®, has been on the market in Europe, Australia, and parts of Asia since January 1998. It is approved as a Class IIb medical device in 41 countries and as a drug in 2 countries. In some countries, the product is registered as Vislube® as a contact lens lubricant, also with a Class IIb medical device designation. The product is currently marketed in 28 countries. Approximately 9.5 million product units were sold during the period between launch in January 1998 and December 31, 2008. It is estimated that approximately 2.8 million patients have used the product during this period, and only 39 reports of medical complaints were related to the product. None of the reported complaints required changes to the product safety labeling.

If SH ophthalmic solution 0.18% is approved for use, adverse reactions and product complaints will be reported to the Medical Information Services group at Alcon Laboratories in Fort Worth, Texas using spontaneous reporting to a toll-free US telephone number (see Package Insert, Appendix 10.2). The Medical Information staff will perform data collection on those issues from consumers and health care professionals and provide the details to the Medical Safety Department at Alcon for investigation. In addition to monitoring adverse reactions and complaints through this mechanism described, the Medical Information Services group will provide product information for healthcare providers and consumers.

A very positive risk-to-benefit ratio has been established for SH ophthalmic solution 0.18% in the treatment of the signs and symptoms of dry eye disease. Numerous studies have demonstrated the mechanism of action of this product in the treatment of dry eye and its efficacy in improving corneal health and reducing many dry eye symptoms. It is the first product to demonstrate statistically significant improvement in both an objective sign and a subjective symptom in two adequate and controlled studies. The efficacy of SH ophthalmic solution 0.18% and its benefit is accompanied by an excellent safety and tolerability profile. The clinical studies were characterized by very low rates of AEs, most of which were not considered related to the study drug, and the existing post-marketing safety data from other countries demonstrate an excellent safety profile. The safety of SH in products used across multiple therapeutic areas via multiple routes of administration, in a variety of patient populations is well established. Sodium hyaluronate is listed as an inactive ingredient in a marketed OTC product in the US.

8. Conclusions

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort and visual disturbance. The disease is caused by tear hyperosmolarity and tear

film instability, which lead to inflammation at the ocular surface. Dry eye disease affects a significant percentage of the population, particularly women over the age of 50 and patients with autoimmune disease. Patients with dry eye disease experience dry-, gritty-, or scratchy-feeling eyes, burning or itching in the eyes, redness, blurred vision, or a sensation of a foreign body in the eye. Symptoms often worsen in dry climates, in windy conditions, with higher temperatures, with lower humidity, and with prolonged use of the eyes (eg, reading, using a computer, or watching television).

A cascade of events is involved in the pathophysiology of dry eye disease. Tear hyperosmolarity causes damage to the surface of the epithelium. The epithelial damage involves cell death, particularly the loss of goblet cells, responsible for secreting mucins onto the ocular surface. The damage to the ocular surface and disruption of mucin production lead to tear film instability. The instability exacerbates the ocular surface hyperosmolarity. This ongoing cycle of dryness and irritation eventually leads to corneal erosion. The erosion exposes nerves, translating into pain.

Goals for treatment of patients with dry eye disease are improvement of ocular comfort and quality of life, and a return of the ocular surface and tear film to a normal homeostatic state. Current therapies are approved for the management of dry eye symptoms, and include tear supplementation, retention and stimulation, anti-inflammatory agents, and environmental strategies (Dry Eye Work Shop, 2007). However, there are currently no products approved by the FDA for the indication of the treatment of the signs and symptoms of dry eye disease.

For approval of a new prescription drug for the treatment of dry eye disease, the FDA requires demonstration of efficacy for both a sign (objective) and a symptom (subjective) of the disease. This criterion has historically been a challenge for new products, and although several new drug candidates have undergone clinical testing in the US for the treatment of dry eye disease, none has yet been approved for this indication. The FDA's requirement for both statistically and clinically significant differences (compared to placebo) on co-primary efficacy endpoints for this indication have been difficult to achieve.

Sodium hyaluronate has unique viscoelastic properties which allow it to behave differently during and between blinks (Bron, 1985; Tiffany, 1994). During blinks, the molecules of SH align with each other and the solution becomes elastic and relatively nonviscous and spreads easily over the surface of the cornea. Between blinks, the molecules of SH form a tangled meshwork, and the solution becomes less elastic and more viscous. This stabilizes the precorneal tear film and maximizes the residence time of the solution on the surface, enabling it to lubricate and protect the ocular surface. Additionally, SH exhibits water entrapping and mucoadhesive properties, which delay its evaporation from the eye surface. These unique

protective properties of this SH ophthalmic solution 0.18% would allow the damaged surface of the dry eye to heal more efficiently.

The substantive efficacy and safety findings provide robust support for regulatory approval of SH ophthalmic solution 0.18% in the treatment of the signs and symptoms of dry eye disease. The study drug is a marketed product in 28 countries with a well-established profile of efficacy and safety, as demonstrated by clinical studies and post-marketing reports. The results of two randomized, controlled Phase 3 clinical studies conducted with SH ophthalmic solution 0.18% show significant benefit in both an objective sign (lissamine green staining) and a subjective symptom (global symptom frequency) with a favorable safety profile. If approved, the SH ophthalmic solution 0.18% proposed would be the first treatment available to patients with dry eye that has demonstrated successful treatment of both an objective sign and a subjective symptom.

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10. Appendices

10.1 Representative Sample of Marketed Products Containing Sodium Hyaluronate/Hyaluronic Acid

Trade Name	Generic Name	Primary Therapeutic Area	Indication/Use	Route(s) of Administration	Organization
Prescription Products Marketed in the US					
Amvisc®	sodium hyaluronate	Ophthalmology	Ophthalmic surgery aid	Injection	Anika Therapeutics, Inc.
Bionect®	hyaluronic acid	Dermatology	Wound/burn dressing/treatment	Topical (gel and cream)	JSJ Pharmaceuticals, Inc.
Deflux™	dextranomer, hyaluronic acid	Genitourinary	For treatment of vesicoureteral reflux in children	Injection	Qmed, Inc. (Health E Monitoring)
Elevess™	hyaluronic acid	Dermatology	For correction of moderate to severe facial wrinkles and folds	Injection	Anika Therapeutics, Inc.; Artes Medical, Inc.; Galderma Laboratories
Euflexxa™	sodium hyaluronate	Musculoskeletal	Osteoarthritis	Injection	Ferring Pharmaceuticals A/S
Gelclair®	polyvinylpyrrolidone, sodium hyaluronate, glycyrrhetinic acid	Pain	Inflammatory diseases, mucositis, pain	Bioadherent oral gel	Cambridge Laboratories Ltd.; Ekr Therapeutics, Inc.; Helsinn Healthcare SA; OSI Pharmaceuticals, Inc. (FKA: Cell Pathways)
Hyalgan®	sodium hyaluronate	Musculoskeletal	Osteoarthritis	Injection	Sanofi Aventis
Hylira™	sodium hyaluronate	Dermatology	Treatment of symptoms associated with xerosis	Topical	Hawthorne Pharma
Juvederm™	hyaluronic acid	Dermatology	Dermatology	Injection	Allergan, Inc.
Nuflexxa	sodium hyaluronate	Pain	Pain	Injection	Ferring Pharmaceuticals A/S; Savient Pharmaceuticals, Inc. (FKA: Bio-Technology General Corp.)

Trade Name	Generic Name	Primary Therapeutic Area	Indication/Use	Route(s) of Administration	Organization
Orthovisc®	sodium hyaluronate	Musculoskeletal	Osteoarthritis	Injection	Anika Therapeutics, Inc.; Depuy Mitek, A Johnson & Johnson Company; Helix Biopharma; Ortho Biotech Products, LP; Surgicraft, Limited; Zimmer, Inc.
Prevelle Silk™	hyaluronic acid	Dermatology	For treatment of facial wrinkles, fine lines, folds, and scars	Injection	Genzyme Corp. (Geltex Pharmaceuticals); Mentor Corp.
Provisc®	sodium hyaluronate	Ophthalmology	Ophthalmic surgical aid	Injection	Alcon Laboratories
Shellgel	sodium hyaluronate	Ophthalmology	Ophthalmic surgical aid	Injection	Anika Therapeutics, Inc.
Solaraze® Gel	diclofenac gel	Dermatology	Actinic keratoses	Gel; topical	Bradley Pharmaceuticals, Inc.; Shire Pharmaceuticals Group, PLC; Skyepharma
Staarvisc ® II	sodium hyaluronate	Ophthalmology	Ophthalmic surgical aid	Injection	Anika Therapeutics. Inc.
Supartz®	sodium hyaluronate	Musculoskeletal	Osteoarthritis	Injection	Smith & Nephew
Suplasyn®	hyaluronic acid	Musculoskeletal	Osteoarthritis	Injection	Bioniche Life Sciences; Recordati S.P.A.
Synvisc®	hyaluronate sodium derivative	Musculoskeletal	Osteoarthritis	Injection	Genzyme Corp. (Geltex Pharmaceuticals); Hoffmann-La Roche, Inc.; Wyeth
XClair™ Cream	sodium hyaluronate	Dermatology	Dermatitis	Topical	Sinclair Pharmaceuticals Limited
Over-the-Counter Products Marketed in the US					
Regenecare	(NA)	Pain and wound healing	Pain and wound healing of skin rashes associated with cancer therapies	Topical	Mpm Medical, Inc.

Trade Name	Generic Name	Primary Therapeutic Area	Indication/Use	Route(s) of Administration	Organization
Blink® Tears	(NA)	Ophthalmology	Temporary relief of burning, irritation, and discomfort due to dryness of the eye or exposure to wind or sun	Ophthalmic drops	Abbott Medical Optics
Products Marketed in Territories Other than the US					
Adant®	hyaluronic acid	Musculoskeletal	Arthritis	Injection	Meda AB
Cystistat®	sodium hyaluronate	Genitourinary	For temporary replacement of the glycosaminoglycan layer in the bladder	Catheter	Bioniche Life Sciences
Durolane®	hyaluronic acid	Musculoskeletal	Osteoarthritis	Injection	Qmed, Inc. (Health E Monitoring)
NeoVisc®	sodium hyaluronate	Musculoskeletal	Osteoarthritis	Injection	Stellar Pharmaceuticals, Inc. (FKA: Stellar International, Inc.)
Sinovial®	sodium hyaluronate	Immune system	Inflammatory diseases	Injection	Institut Biochemique Sa (Ibsa)
Suplasyn®	hyaluronic acid	Musculoskeletal	Musculoskeletal	Injection	Bioniche Life Sciences; Recordati S.P.A.
Vismed® *	sodium hyaluronate ophthalmic solution 0.18%	Ophthalmology	Ophthalmic solution for relief of dry eye associated with contact lens wear or environmental factors	Ophthalmic drops	TRB Chemedica, AG
Vislube® *	sodium hyaluronate ophthalmic solution 0.18%	Ophthalmology	Ophthalmic solution for relief of dry eye associated with contact lens wear or environmental factors	Ophthalmic drops	TRB Chemedica, AG
Hylovis® *	sodium hyaluronate ophthalmic solution 0.18%	Ophthalmology	Ophthalmic solution for relief of dry eye associated with contact lens wear or environmental factors	Ophthalmic drops	TRB Chemedica, AG

Abbreviations: FKA = Formerly known as; NA = Not applicable; US = United States.

Note: The information presented was obtained from BioPharm Insight, Drug Topics Red Book, and information available in the public domain.

* Branded versions of the proprietary formulation of sodium hyaluronate ophthalmic solution 0.18% proposed for approval in the US under NDA 22-358.

10.2 Proposed Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use REJENA (sodium hyaluronate ophthalmic solution), 0.18% safely and effectively. See full prescribing information for REJENA.

REJENA (sodium hyaluronate ophthalmic solution), 0.18%

Initial US Approval: 2009

---------INDICATIONS AND USAGE----------

REJENA is a glycosaminoglycan indicated for the treatment of the signs and symptoms of dry eye disease. (1)

------DOSAGE AND ADMINISTRATION------

Instill one to two drops of REJENA into both eyes four times daily. (2)

-----DOSAGE FORMS AND STRENGTHS----

REJENA is a sterile ophthalmic solution containing sodium hyaluronate 0.18% and is provided in a single use vial containing 0.3mL. (3)

----------CONTRAINDICATIONS----------

Known or suspected hypersensitivity to any of the ingredients of this preparation. (4)

--------WARNINGS AND PRECAUTIONS-------

For topical ophthalmic use only. (5)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥1%) were dry eye, eye pain, eye irritation, foreign-body sensation, reduced visual acuity, eye pruritis, blurred vision, ocular hyperemia, and eyelid margin crusting.

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9195 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: [mm/yyyy]

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

REJENA (sodium hyaluronate ophthalmic solution), 0.18% is indicated for the treatment of the signs and symptoms of dry eye disease.

2 DOSAGE AND ADMINISTRATION

Instill one to two drops of REJENA into both eyes four times daily.

3 DOSAGE FORMS AND STRENGTHS

REJENA is a sterile ophthalmic solution containing sodium hyaluronate 0.18% and is provided in a single use vial containing 0.3mL.

4 CONTRAINDICATIONS

Known or suspected hypersensitivity to any of the ingredients in the formula or to other hyaluronate acid-containing medications.

5 WARNINGS AND PRECAUTIONS

For topical ophthalmic use only.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Three, randomized, controlled, parallel-group trials, two of which were multicenter investigations, were conducted in 616 patients with dry eye disease. Study 1 compared REJENA to vehicle (REJENA, n=221; vehicle, n=223), Study 2 compared REJENA to topical saline (REJENA, n=74; saline, n=77), and Study 3 compared REJENA to sodium carboxymethylcellulose 1% eye drops (REJENA, n=10; carboxymethylcellulose, n=11). Table 1 presents the most common adverse reactions (≥1%) that occurred in patients treated with REJENA.

Table 1. Summary of Adverse Reactions Occurring in ≥1% of Patients

Adverse Event	Study 1		Study 2		Total Patients
	REJENA (N=221)	Vehicle (N=222[a])	REJENA (N=74)	Saline (N=77)	REJENA (N=305[b])
Dry eye	18 (8.1%)	14 (6.3%)	0	0	18 (5.9%)
Eye pain	13 (5.9%)	7 (3.2%)	0	0	13 (4.3%)
Eye irritation	4 (1.8%)	5 (2.3%)	2 (2.7%)	0	6 (2.0%)
Foreign-body sensation	5 (2.3%)	7 (3.2%)	0	0	5 (1.6%)
Eye pruritus	4 (1.8%)	4 (1.8%)	0	0	4 (1.3%)
Visual acuity reduced	4 (1.8%)	6 (2.7%)	0	0	4 (1.3%)
Vision blurred	4 (1.8%)	0	0	0	4 (1.3%)
Ocular hyperemia	3 (1.4%)	3 (1.4%)	0	0	3 (1.0%)
Eyelid margin crusting	3 (1.4%)	1 (0.5%)	0	0	3 (1.0%)

[a] One patient in the vehicle group did not receive study drug, therefore was excluded from the safety analysis.
[b] Includes patients treated with REJENA in Study 3 (N=10), in which there were no AEs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at doses of 50 mg/kg and have revealed no evidence of impaired fertility or harm to the fetus due to administration of sodium hyaluronate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should only be used during pregnancy if clearly needed.

8.3 Nursing Mothers

Caution should be exercised when REJENA is administered to a nursing woman.

8.4 Pediatric Use

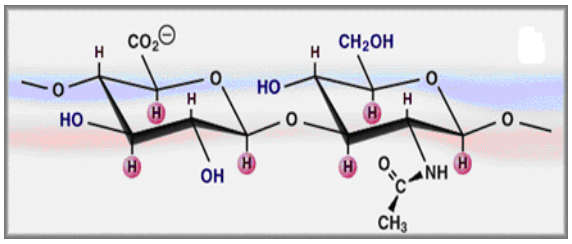
Safety and effectiveness of REJENA in pediatric patients have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness of REJENA have been observed between elderly and younger patients.

11 DESCRIPTION

REJENA (sodium hyaluronate ophthalmic solution), 0.18% is a sterile solution for ophthalmic use. Hyaluronic acid, which can form a variety of salts, including sodium hyaluronate, is also described as hyaluronic acid sodium salt or hyaluronan. Sodium hyaluronate is represented by the following structural formula.



Sodium hyaluronate is a polymer produced by bacterial fermentation and purification. The fermentation process allows for a high degree of control for achieving sodium hyaluronate in a relatively narrow range of molecular weights. The molecular weight is important as it is correlated to the intrinsic viscosity of the product. Intrinsic viscosity is a measure of the capability of a polymer in solution to increase the viscosity of the solution. It is the viscosity that gives REJENA its characteristic long residence time on the surface of the eye. The fraction used in REJENA is characterized by an intrinsic viscosity in the range of 18.0 to 24.0 dL/g (corresponding to 1.8 to 2.4 m^3/kg).

The empirical formula for sodium hyaluronate is $(C_{14}H_{20}O_{11}N_1Na_1)_n$.

Each mL contains: ACTIVE: sodium hyaluronate 1.8 mg; INACTIVES: calcium chloride, dibasic sodium phosphate, magnesium chloride, potassium chloride, sodium chloride, sodium hydroxide, sodium citrate, water for injection, and hydrochloric acid to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sodium hyaluronate is a polysaccharide (glycosaminoglycan) consisting of a sequence of disaccharide units, linked to each other by a β1—>3 bond. This disaccharide unit repeats itself, forming a linear chain of high molecular weight which, in physiological saline solution, assumes a random coil configuration characterized by a large hydration volume. The sodium hyaluronate used in REJENA is obtained by bacterial fermentation and purification and is comprised of a specific fraction with a high degree of purity.

The most important property of sodium hyaluronate is its viscoelasticity. This physicochemical property mechanistically leads to the following actions after topical instillation to the eye: 1) During blinking, shear stress causes the sodium hyaluronate molecules in solution to align with one another; as a result, the solution becomes elastic and relatively nonviscous, and spreads easily over the surface of the cornea. 2) Between blinks, the molecules of sodium hyaluronate form a tangled meshwork, and the solution becomes less elastic and more viscous; consequently, the precorneal tear film is stabilized and the residence time of the solution on the surface is maximized.

Due to the coiled structure of the sodium hyaluronate molecule, REJENA is highly effective in entrapping water. With effective water entrapment, the rate of tear evaporation is slowed. Sodium hyaluronate solutions adhere to the mucin layer of the precorneal tear film.

These physicochemical properties of the molecule, together with observed pharmacodynamic effects, such as increased corneal wound healing, ameliorate the signs and symptoms typically associated with dry eye disease.

12.2 Pharmacodynamics

Sodium hyaluronate promotes migration of human corneal epithelial cells in vitro, leading to beneficial effects on corneal wound healing.

12.3 Pharmacokinetics

No nonclinical pharmacokinetic studies have been conducted with REJENA, although sodium hyaluronate has been investigated extensively. High molecular weight molecules such as sodium hyaluronate are not expected to pass through the conjunctiva and the corneal epithelium. Data from intraocular administration (anterior chamber injection) in rats and rabbits indicate that the $t_{1/2}$ for elimination of sodium hyaluronate (mw 2.8 million D) from the aqueous humor was approximately 10.5 hours and that no product is detected 24 hours after administration. Low blood levels of ^{14}C-labelled material were found during the 72-hour period after intraocular administration, with a maximal blood level of 1 µg/mL in plasma, which represent about 2.5% of the injected dose. Numerous studies have been performed with sodium hyaluronate using oral, intravenous, intratracheal, and aerosolized inhalation deliveries. Sodium hyaluronate administered parenterally in animals indicated that the molecule is quickly metabolized ($t_{1/2}$=2.5 to 5.5 minutes), and is rapidly removed from the bloodstream and degraded in the liver.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No maternal toxicity, fetal toxicity, or teratogenic effects on the fetuses of treated dams (rats or rabbits) has been observed after subcutaneous sodium hyaluronate administration at doses up to 50 mg/kg/day. Sodium hyaluronate has shown no mutagenic or clastogenic potential in bacterial assays and cytogenetic assays conducted both in vitro and in vivo.

Long-term studies have not been conducted to evaluate the carcinogenic potential of sodium hyaluronate.

13.2 Animal Toxicology and/or Pharmacology

Hyaluronic acid (sodium hyaluronate) is a biological substance that is ubiquitous in mammalian connective tissues, including vitreous body and synovial joints. Purified hyaluronic acid produced by fermentation does not show appreciable toxicity or sensitization. The results of nonclinical toxicity studies conducted with REJENA and sodium hyaluronate obtained by fermentation showed no cytotoxic effect on conjunctival cells in vitro; no toxic effects following acute and subacute topical ocular administration in albino rabbits and rabbits with pigmented eyes; no acute toxic effects following injection into the anterior chamber or vitreous body of monkey eyes; and no acute toxic effects in mice or rats following oral, intraperitoneal, or subcutaneous administration. Chronic administration studies of sodium hyaluronate in rats or dogs following subcutaneous administration showed no toxic effects, with the exception of local tissue hardening and/or edema at the injection site which was reversible. No antigenicity was detected in guinea pigs, mice, or rabbits after parenteral administration.

14 CLINICAL STUDIES

Two multicenter, randomized, controlled, double-masked, parallel-group, Phase 3 trials were conducted in 595 patients with dry eye disease. Study 1 compared REJENA to vehicle (REJENA, n=221; vehicle, n=223), and Study 2 compared REJENA to topical saline (REJENA, n=74; saline, n=77). Efficacy analyses were conducted for Days 7 and 14 compared to Day 0 (baseline) for Study 1 and for Days 7 and 28 compared to Day 0 (baseline) for Study 2.

Efficacy Endpoints

The objective efficacy endpoint, change in lissamine green staining scores, assessed treatment effect on a *sign* of dry eye disease, the integrity of the cornea. The subjective efficacy endpoint, change in global symptom frequency scores, assessed treatment effect on a composite of *symptoms* of dry eye disease (soreness, scratchiness, dryness, grittiness, and burning). The results of these endpoints for Study 1 and Study 2 are summarized in Tables 2 and 3. The primary time points were Day 7 for Study 1 and Days 7 and 28 for Study 2.

Table 2. Change From Baseline in Lissamine Green Staining Scores in the Study Eye

Visit	Treatment	Study 1		Study 2	
		Mean (SD)	***P t-test***	**Mean (SD)**	***P t-test***
Day 0	REJENA	5.71 (2.421)	0.4132	4.03 (2.120)	0.5857
	Control	5.52 (2.357)		3.83 (2.279)	
Day 7	REJENA	-1.1 (2.01)	**0.0291**	-1.1 (1.51)	**0.0237**
	Control	-0.7 (1.79)		-0.6 (1.38)	
Day 14/ Day 28[a]	REJENA	-1.4 (1.91)	**0.0243**	-1.6 (1.67)	**0.0144**
	Control	-1.0 (1.81)		-0.9 (1.46)	

[a] Day 14 in Study 1 and Day 28 in Study 2.

In both Study 1 and Study 2, the mean changes from baseline in lissamine green staining scores were statistically significantly greater in the REJENA treatment group versus the placebo treatment group at Day 7, demonstrating that REJENA effectively treats a *sign* of ocular surface injury within seven days and has a sustained effect.

Table 3. Change From Baseline in Global Symptom Frequency Scores in the Study Eye

Visit	Treatment	Study 1		Study 2	
		Mean (SD)	*P t-test*	Mean (SD)	*P t-test*
Day 0	REJENA	8.33 (2.231)	0.06208	8.35 (2.272)	0.3477
	Control	8.22 (2.470)		8.04 (1.758)	
Day 7	REJENA	-1.7 (2.78)	**0.0173**	-2.0 (2.44)	**0.0470**
	Control	-1.1 (2.62)		-1.2 (2.58)	
Day 14/ Day 28[a]	REJENA	-2.4 (2.91)	0.2202	-2.9 (2.29)	**0.0134**
	Control	-2.1 (2.92)		-1.8 (2.81)	

[a] Day 14 in Study 1 and Day 28 in Study 2.

In Study 1 and Study 2, the REJENA treatment group showed a statistically significantly greater mean change from baseline in global symptom frequency scores (soreness, scratchiness, dryness, grittiness, and burning) at Day 7 in the REJENA treatment group versus the vehicle treatment group. Additionally, in Study 2, a statistically significantly greater mean change from baseline in global symptom frequency scores was observed for the REJENA treatment group versus the saline treatment group at Day 28. These data demonstrate that REJENA effectively treats a *symptom* of dry eye disease within seven days and has a sustained effect.

16 HOW SUPPLIED/STORAGE AND HANDLING

REJENA (sodium hyaluronate ophthalmic solution), 0.18% is supplied as low-density polyethylene, single use vials, each containing 0.3 mL of sterile, 0.18% sodium hyaluronate solution. Four strips of 5 single unit vials are packed in a sealed, laminated aluminum foil pouch.

A carton contains six pouches of twenty 0.3 mL unit vials for a total of 120 single unit vials. (NDC xxxxx-xxx-xx)

Storage: Store at 15°C–25°C (59°F–77°F). Protect from light. Do not freeze.

17 PATIENT COUNSELING INFORMATION

17.1 Avoiding Contamination of the Product

This product is sterile when packaged. The solution from one individual single use vial is to be used to instill REJENA into both eyes immediately after opening. The used vial and any remaining REJENA should be discarded immediately.

The product is manufactured for:

Alcon Laboratories, Inc.
Fort Worth, Texas 76134
USA

by:

Holopack Verpackungstechnik GmbH
74429 Sulzbach-Laufen
Germany

10.3 Protocol Summaries

10.3.1 Baudouin 2005 Study

10.3.1.1 Protocol Summary

Study Title:	A Double-blind, Randomized, Saline-Controlled, Multicentre, Parallel-group, Phase 3 Study on SVS20 in Patients with Bilateral Moderate Dry Eye Syndrome (Disease)
Study Number:	SVS20-99-04 (also referred to as "Baudouin 2005")
Study Phase:	3
Product Name:	Sodium Hyaluronate Ophthalmic Solution 0.18% (SVS20)
IND Number:	73,441
Indication:	Dry eye syndrome (disease)
Investigators:	Multicenter
Sponsor:	Chemedica SA
Sponsor Contact:	Vincent Baeyens, PhD
Sponsor's Legal Representative:	J.P. Bauloz, Director Chemedica SA Chemin St. Marc No. 3 1896 Vouvry, Switzerland
Medical Monitor:	Dr. Nguyen My-Lam, MD

	Date
Original Protocol:	July 19, 2000
Revision:	December 7, 2000
	February 10, 2001
	September 6, 2002
	October 6, 2002

Sponsor:
Chemedica SA

Name of Finished Product:
Sodium hyaluronate ophthalmic solution 0.18% (known as SVS20, Vismed®, Vislube®, and Hylovis®)

Name of Active Ingredient:
Sodium hyaluronate

Study Title:
A Double-blind, Randomized, Saline-Controlled, Multicentre, Parallel-group, Phase3 Study on SVS20 in Patients with Bilateral Moderate Dry Eye Syndrome (Disease)

Study Number:
SVS20-99-04 (also referred to as Baudouin 2005)

Study Phase: 3

Primary Objective(s):
To compare the efficacy of sodium hyaluronate ophthalmic solution 0.18% to saline in subjects with bilateral dry eye disease

Secondary Objective(s):
To compare the safety of sodium hyaluronate ophthalmic solution 0.18% to saline in subjects with bilateral dry eye disease

Study Design:
Phase 3, multicenter, randomized, controlled, double-masked study of the safety and efficacy of sodium hyaluronate ophthalmic solution 0.18% vs saline in subjects with dry eye disease

Study Population:
A total of 136 subjects with dry eye will be included in the study in 15 centers with a minimum of 8 subjects per center. The subjects will be randomly assigned to treatment with SVS20 or saline using a randomization table.

Subjects meeting the following criteria will be **enrolled** in the study:

1. Male and female subjects aged 18 years and over
2. Subjects with at least a 3-months documented history of moderate dry eye
3. Female subjects should be post-menopausal or be using a recognized, reliable method of contraception for at least 3 months before the Day -5 visit
4. Subjects experiencing at least two symptoms of bilateral dry eye among soreness, scratchiness, dryness, grittiness, and burning
    - at least occurring often, and
    - at least rated 50 mm on the Visual Analogue Scale (VAS) scale (*changed to 40 mm by Protocol Amendment; 54 of 136 subjects enrolled under original criterion*)
5. At least three out of the four following objective parameters:
    - reduced tear volume: Shirmer test ≤ 10 mm wetting/5 minutes for each eye
    - tear film instability: tear film break-up time (TBUT) ≤ 10 seconds for each eye
    - staining with fluorescein with a total score ≥ 3 for each eye
    - staining with lissamine green with a total score ≥ 3 for each eye

6. If the subject takes the following medications, he/she should have taken these products continuously for the 2 months before the Day -5 visit:
    - Tricyclic antidepressives
    - Anti-histaminics
    - Phenothiazines
    - Cholinergics
    - Anti-muscarinics
    - Non-steroidal anti-inflammatory drugs (NSAIDs)
    - Corticosteroids
    - Beta-blockings
    - Immunomodulators
    - Anti-acnes
    - Diuretics
7. If the subject is a contact lens wearer, he/she mustn't wear his/her lenses for the duration of the study.

Subjects who meet any of the following criteria will be **excluded** from the study:

1. Subjects with unilateral dry eye
2. Pregnant or lactating females
3. Severe dry eye syndrome, defined as:
    - Staining with fluorescein with a depth score ≥ 3 and/or
    - Severe bulbar conjunctival hyperaemia (score of 4) and/or
    - Severe limbal hyperaemia (score of 4) and/or
    - Severe palpebral observation (score of 4) and/or
    - Severe blepharitis
4. Ocular surgery (whatever type) or ocular trauma within the last 4 months before inclusion
5. Abnormality of the nasolacrimal drainage apparatus
6. Subject with permanent occlusion of lacrimal puncta in any eye
7. Use of temporary punctual plug within 2 months before the Day -5 visit in any eye.
8. Other diseases or characteristics judged by the investigator to be incompatible with the frequent assessments needed in this study or with reliable instillation of the products (eg, disability of the upper limbs)
9. Subject not subscribed to the social security system in France
10. Participation in any other clinical study within the last 30 days
11. Known hypersensitivity to hyaluronic acid or any component or procedure used in the study
12. Wearing of contact lens during the whole study

Test Product, Dose, and Mode of Administration:
One drop of sodium hyaluronate ophthalmic solution 0.18% or saline, as allocated, will be instilled into each eye at least 3 and up to 8 times daily.

Duration of Treatment:
28 days

Efficacy Assessments: Fluorescein staining of the cornea; lissamine green staining of the conjunctiva and cornea; Schirmer I testing; rating of symptom frequency; global scoring of symptom intensity by VAS; composite index of symptom intensity and frequency; tear prism height, TBUT, slit lamp biomicroscopy examination, flow cytometry, comfort of the eye drops, and repercussion of dry eye symptoms on daily life (see Sections 5.2.1.1 and 5.2.1.2). See Schedule of Events for details).
Safety/Tolerability Assessments: General external ophthalmic examination, far visual acuity, slit lamp biomicroscopy examination, and collection of adverse events (AEs; see Section 6). See Schedule of Events for details.
Statistical Methods: The primary efficacy endpoint (subjective measure) will be the percent change from baseline of the final VAS summed score (sum of five VAS symptom scales for soreness, scratchiness, dryness, grittiness, and burning) at Day 28. The co-primary efficacy measure (objective measure) will be percent change from baseline of the final fluorescein staining summed score (sum of the total scores over both eyes) of the cornea at Day 28. The primary objective and primary subjective analysis will assess the significance of the difference between sodium hyaluronate ophthalmic solution 0.18% and control (saline placebo) with respect to change from baseline at Day 28 using a one-sided Wilcoxon-Mann-Whitney test for superiority (alpha level of 0.025). The sample size estimates were calculated based on the ongoing Phase 2 study, SVS20-99-01 (*also referred to as Baudouin 2001*). The study will have power of 98.0% to yield a statistically significant result. The calculated sample size is a total of 136 subjects, to be randomized equally into the two treatment groups; sodium hyaluronate ophthalmic solution 0.18% (active) or saline (placebo).

10.3.1.2 Subject Randomization and Study Assessments

Study evaluations will be conducted at Screening, baseline, and two treatment phase visits, according to the Schedule of Events. Screening assessments will be conducted between 12 and 4 days prior to baseline assessments (Day -12 to Day -4) and randomization into the study.

At the Screening visit, subjects will be asked to respect a wash-out period until their return for baseline evaluation at Day 0. During the wash-out period, subjects will be asked to use Unilarm® drops (saline solution) as it would be unethical not to provide any relief eye drop to the subjects. At the same visit, subjects will be asked to discontinue use of Unilarm® for at least 4 hours before the baseline assessments and not to wear contact lenses during the entire study.

At the Day 0 visit, subjects who continue to meet the study criteria will be randomized into the study. Study medications will be dispensed according to the randomization code and treatment phase assessments will occur at Days 7 and 28 according to the Schedule of Events. Thereafter, any AEs persisting through the end of the study (Day 28) will be

followed up by the investigator until satisfactory resolution, or until no further information is available.

10.3.1.3 Treatment

At Day 0, after all the baseline examinations have been performed, the subject will apply one drop of the allocated product into each eye and blink several times to allow the solution to spread over the cornea (in the presence of the investigator). He/she will be instructed to repeat administrations at least 3 times a day. Depending on the comfort and symptoms experienced, he/she may use up to a maximum up to 8 applications per day for 28 days. The subject will be instructed to treat both eyes, using the same monodose.

10.3.1.4 Efficacy Assessments

10.3.1.4.1 Objective Efficacy Measures

Fluorescein Staining

Fluorescein 0.5% solutions will be placed on the inferior palpebral conjunctiva. The subjects will be asked to blink several times and move their eyes around to thoroughly mix the fluorescein with the tear film. The cornea will be examined 3 minutes after instillation through a biomicroscope containing a Wratten No. 12 barrier filter. Staining will be graded on a 4-point scale for 3 characteristics. Fluorescein staining will be performed at all study visits (see Schedule of Events).

1. Type
   - 0 = No staining
   - 1 = Micropunctate
   - 2 = Macropunctate
   - 3 = Coalescent macropunctate
   - 4 = Patch

2. Extent/Surface Area
   - 0 = 0%
   - 1 = 1%–15%
   - 2 = 16%–30%
   - 3 = 31%–45%
   - 4 > 45%

3. Depth (based on penetration of fluorescein and slit lamp optic section)
   - 0 = No staining
   - 1 = Superficial epithelium
   - 2 = Deep epithelium, delayed stromal glow
   - 3 = Immediate localized stromal glow
   - 4 = Immediate diffuse stromal glow

The investigator will record the global score (type + extent + depth, maximum score is 12) in the Case Report Form (CRF).

Lissamine Green Staining of the Cornea and Conjunctiva

Lissamine green staining test will be performed after instillation of one drop of a 1% solution of lissamine green. The areas evaluated will be the cornea and the nasal and temporal conjunctiva. Each area will be graded as follows:

0 = 0%
1 = 1%–15%
2 = 16%–30%
3 = 31%–45%
4 = >45%

The investigator will record the global score (maximum score is 12) in the CRF. Lissamine green staining will be performed at all study visits (see Schedule of Events).

Schirmer I Test

The Schirmer I test will be performed without anesthesia using a Whatman No. 41 paper. The test will be done without touching the paper strip directly with the finger to avoid contamination with skin oils. The strip will be placed at the junction of the middle and lateral one-third of the lower eye lid. The subject will be told to look forward and to blink normally while a strip is placed in the right eye and one in the left eye. Strips will be removed after five minutes and the amount of wetting is recorded in mm. The Schirmer I test will be performed at all study visits (see Schedule of Events).

Tear Prism Height

Tear prism height (mm) will be assessed semi-quantitatively with slit lamp (0.5, 1.0, 1.5, 2.0, 2.5, or 3.0 mm). Tear prism height will be performed at all study visits (see Schedule of Events).

Tear Film Break-up Time

When fluorescein is uniformly spread onto the eye surface, subject will be asked first to close and then open his/her eyes. The time from opening of the examined eye to the appearance of the first dry spot will be measured. The results of three measurements and the mean of these values will be recorded in the CRF. TBUT will be performed at all study visits (see Schedule of Events).

Slit lamp biomicroscopy examination

The following will be assessed at each study visit (see Schedule of Events):

Limbal hyperaemia:
0 = None (no hyperaemia)
1 = Trace (slight limbal [mild segmented])
2 = Mild (mild limbal [mild circumcorneal])
3 = Moderate (significant limbal [marked segmented])
4 = Severe (severe limbal [marked circumcorneal])

Bulbar conjunctival hyperaemia:
0 = None (no hyperaemia)
1 = Trace (slight regional hyperaemia)
2 = Mild (diffuse hyperaemia)
3 = Moderate (marked regional or diffuse hyperaemia)
4 = Severe (diffuse episcleral or sclera hyperaemia)

Palpebral conjunctival observations:
0 = None (uniform satin appearance of the conjunctiva)
1 = Trace (slight conjunctival injection without texture)
2 = Mild (mild or scattered papillae/follicles less than 1 mm in diameter)
3 = Moderate (significant papillae/follicles less than 1 mm in diameter and/or marked conjunctival injection), or Moderate (staining of the top of one papilla)
4 = Severe (localized or generalized papillae/follicles 1 mm or more in diameter), or Severe (staining of the top of more than one papilla)

Flow cytometry

The flow cytometry will be assessed on the right eye of 20 subjects in 3 centers (Investigators; Baudouin, Laroache, and Garcher), and will be performed at Days 0 and 28 (see Schedule of Events).

Flow cytometry on specimens of impression cytology allows quantitative assessments of goblet (mucus producing) cells and inflammatory cells. It is performed after immunofluorescence staining which is a modification of the classical impression cytology where the cells were identified *de visa* after direct staining. In the present test, inflammatory cells will be identified by the antibodies directed against class II antigens (anti-HLA DR from Dako and anti-CD40 from Beckman) while mucus cells will be identified by antibodies recognizing mucus producing cells (anti-MUC1, from INSERM St. Antoine, Dr. Jaques Bara).

Collection of the specimens

The collection of the conjunctival cytologic specimens and the immunostaining procedure used are published in detail. In brief, the specimens will be collected more than 15 minutes after the last dye test. After application of one drop of contact anesthetic, two polyether sulfone filter membranes will be applied successively, without exerting any pressure, onto the superior and superotemporal bulbar conjunctiva, in two different but neighboring areas. Care will be taken to collect specimens only in non-exposed regions of the conjunctiva. Membranes will be removed immediately after contact. If a specimen is not readily visible, a new one will be collected in another area. The membranes will be put into cold fixative provided by the Laboratory of immunohematology.

Flow cytometry

The membranes will be left in 2 mL of phosphate buffered saline, gently agitated for 30 minutes, and centrifuged (200 *g*, 5 minutes). The specimen will be incubated first with mouse monoclonal antibodies (HLA DR, CD40, CD44, and MUC1); then, after washing, with a fluorescein-conjugated anti-mouse immunoglobulin. Cell suspensions will be analyzed on a flow cytometer (FACScan, Becton Dickinson).

The number of antigen-positive conjunctival cells (mucus or inflammatory cells) will then be obtained from a cytogram representing mean fluorescence intensities. The percentage of positive cells to the markers will be calculated. For each antibody at least 1000 cells will be analyzed, the threshold for reliable determinations. Poorer specimens will not be analyzed.

Quantification of fluorescent antibodies binding to conjunctival cells will also be determined by translating the mean fluorescence intensities observed on fluorescence histograms into standardized fluorescence units (arbitrary units of fluorescence). This is done using a calibration curve established with calibrated beads (Immunobrite®, Coulter).

The specimens will be assessed by one examiner (Dr. Françoise Brignole, MD, Hôpital Ambroise Paré), in a masked manner.

10.3.1.4.2 Subjective Efficacy Measures

Symptoms

A 100 mm VAS (0 = no symptom to 100 = severe symptom) will be used at each visit to assess the evolution of the *intensity* of symptoms, including soreness, scratchiness, dryness, grittiness, and burning. The investigator will measure the distance from the 0 point on the VAS scale in mm and record the result on the CRF. The *frequency* of symptoms will be assessed according to the rating scale; “never,” “sometimes,” “often,” or “constantly.” A global score for both eyes for both parameters will be recorded at each study visit (see Schedule of Events).

Repercussion of Symptoms on Daily Life

Rating of repercussion of the dry eye syndrome on screen work or television watching, reading, driving will be performed at each visit as follows:

0 = Absent
1 = Minimal
2 = Moderate
4 = Severe

A global score for both eyes will be recorded at each study visit (see Schedule of Events).

Comfort of the eye drops

Comfort after application will be rated at each visit as follows:

0 = Good
1 = Moderate
2 = Bad

Both description and duration of the sensation will be recorded. A global score for both eyes will be recorded. This parameter will be assessed at Days 7 and 28 only (see Schedule of Events).

10.3.1.5 Safety Assessments

The following will be assessed on each eye:

General External Ophthalmic Examination

Characterization of symptoms (including impairment of dry eye symptoms) and examination of ocular adnexa (eye lids and periocular area) by gross inspection and palpation will be assessed at each study visit (see Schedule of Events).

Far Visual Acuity

Corrected far visual acuity, using LogMAR progression charts, will be evaluated at Days 0 and 28 study visits. Values will be recorded in decimal values.

Slit lamp Biomicroscopy Examination

The findings of this measure for efficacy will also assess the tolerance in the event there is a worsening of signs not attributable to the normal evolution of the pathology. This evaluation will be performed at each study visit (see Schedule of Events).

Adverse Events Assessments

Occurrence of AE is monitored throughout the study at all visits (see Schedule of Events). All AEs observed during the study period, including those which occurred during the Screening period and at baseline visits (Day -12 through Day 0), will be recorded in the appropriate section of the CRF. Diseases, clinical indications, and symptoms and/or pathological laboratory values detected at the Screening or baseline visits are not recorded as AEs if encountered at a later visit unless a deterioration or increased frequency is observed.

All AEs, regardless of severity and whether or not they are ascribed to the study treatment, will be recorded in the appropriate section of the CRF using standard medical terminology.

If no AE has occurred, this will be noted in the appropriate place on the AE section of the CRF.

Definition of an Adverse Event

An AE is any undesirable event occurring with the use of the test products, whether or not considered related to their use, and includes any reaction, including changes in laboratory parameters (not routinely assessed in this study), which does not commonly occur in the included subjects. In this study, this means that any score of 4 at slit lamp examination, and a depth score of 3 or 4 at corneal staining examination with fluorescein, corneal ulceration, corneal or conjunctival infection, severe inflammation (conjunctivitis, iritis,), corneal scarring will be AEs.

Performing Adverse Events Assessments

All AEs either observed by the investigator or reported by the subject during the study (including the period between visits) will be evaluated in order to assess the tolerability of the product. AEs will be assessed at each post-randomization study visit (ie, once subjects receive the first dose of study drug [Days 0, 7, and 28]); evaluation of AEs will be assessed relative to the Screening and baseline AEs recorded.

AEs will be assessed according to the following criteria and entered in the CRF: date of onset; duration; nature; measures taken; intensity (mild, moderate, severe); relationship to study drug; and outcome. The investigator will also record whether the event was serious and/or unexpected. All AEs, regardless of severity, will be followed by the investigator until satisfactory resolution, or until no further information is available, but at least until the end of the study.

Evaluation of Severity

The investigator will use the following definitions to code the intensity of the event:

mild usually transient, requiring no special treatment, and does not interfere with the subject's daily activities

moderate	traditionally introduces a low level of inconvenience or concern to the subject and may interfere with daily activities, but is usually relieved by simple therapeutic measures
severe	causes an interruption of the subject's usual daily activity and traditionally requires systemic drug therapy or other treatment

There is a distinction between the severity and the seriousness of an AE. Severe is a measurement of intensity; thus, a severe reaction is not necessarily a serious AE (SAE). For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for SAEs (see Serious Adverse Events).

Relationship

The following categories were used to classify the relationship between AEs and the study drug:

not related	evidence indicates no plausible direct relationship to the study medication
unlikely related	suggests other conditions are reasonably likely to account for the event including concurrent illness, progression, or expression of the disease state, or reaction to concurrent medication
possibly related	suggests that the association of the event with the study medication is unknown; however, the AE is not reasonably supported by other conditions
related	follows anticipated response to study medication and is confirmed by discontinuing and/or rechallenge

The causality rating of AEs will be determined during the examination by the investigator under masked conditions, except when the seriousness or causality of the AE warrants breaking the randomization code.

Expectedness

An unexpected adverse event is defined as any event that is not identified in nature, severity or frequency in the current version of the Investigator's Brochure (IB).

Serious Adverse Events

Definition

An SAE is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth

defect. In this study, permanent loss of vision will be considered serious and thus require immediate report.

All AEs classified by the investigator as serious will be reported to the sponsor immediately (see Reporting of Serious and Unexpected Adverse Events). SAEs related to study drug must be reported to the Ethical Committee and to the Sponsor, which will report the event to the French authority body.

SAEs occurring after completion of the study, but are justifiably considered by the investigator to be related to study drug, must also be reported to the Sponsor.

Reporting of Serious and Unexpected Adverse Events

The investigator will inform the Sponsor of every serious or unexpected AE within 24 hours of its occurrence. The information must be communicated by telephone or facsimile. The "Serious Adverse Event Form" must be completed and sent to the sponsor within 3 days following the event.

10.3.1.6 Schedule of Events

PROCEDURES & ASSESSMENTS	VISITS DAY			
	-5[a]	0	7	28
Verification of inclusion and exclusion criteria	X	X		
Informed consent	X			
Drug accountability		X	X	X
Relevant previous and concomitant medications	X	X	X	X
Symptoms intensity on Visual Analogue Scale (VAS)	X	X	X	X
Symptoms frequency	X	X	X	X
Repercussion of symptoms on daily life	X	X	X	X
Comfort of the eye drops			X	X
Far visual acuity (corrected)		X		X
General External Ophthalmic Examination	X	X	X	X
Slit lamp biomicroscopy examination	X	X	X	X
Tear prism height	X	X	X	X
Schirmer I test	X	X	X	X
Tear film break-up time (TBUT)	X	X	X	X
Fluorescein staining	X	X	X	X
Lissamine green staining	X	X	X	X
Flow cytometry[b]		X		X
First administration of the assigned treatment		X		
Adverse event (AE) report		X	X	X

a. Screening is to occur in the range of Day -12 to Day -4.

b. Assessment to be performed on 20 subjects, enrolled at 3 centers only (investigators; Baudouin, Laroache, and Garcher)

10.3.2 Study RP-001

10.3.2.1 Protocol Summary

Study Title:	A Phase 3 Multicenter, Randomized, Controlled, Double-Masked Study of Safety and Efficacy of Vismed® in Dry Eye Syndrome (Disease)
Study Number:	RP-001
Study Phase:	3
Product Name:	Sodium Hyaluronate Ophthalmic Solution 0.18%
IND Number:	73,441
Indication:	Dry eye syndrome (treatment of the signs and symptoms of dry eye disease)
Investigators:	Multicenter
Sponsor:	River Plate Biotechnology, Inc.
Sponsor Contact:	Terry W. Laliberte
Sponsor's Legal Representative:	Luis Molina 100 Europe Drive, Suite 421, Chapel Hill, NC 27517
Medical Monitor:	Roger Vogel, MD

	Date
Original Protocol:	June 6, 2006
Revision:	August 18, 2006 October 16, 2006 March 7, 2007 March 20, 2008

Sponsor:
River Plate Biotechnology, Inc.

Name of Finished Product:
Sodium hyaluronate (SH) ophthalmic solution 0.18% (known as SVS20, Sodium Hyaluronate Ophthalmic Solution 0.18%Vismed®, Vislube®, and Hylovis®)

Name of Active Ingredient:
Sodium hyaluronate

Study Title:
A Phase 3 Multicenter, Randomized, Controlled, Double-Masked Study of Safety and Efficacy of Vismed® in Dry Eye Syndrome (Disease)

Study Number:
RP-001

Study Phase: 3

Primary Objective(s):
To compare the efficacy of SH ophthalmic solution 0.18% to vehicle in subjects with dry eye disease

Secondary Objective(s):
To compare the safety of sodium hyaluronate ophthalmic solution 0.18% to vehicle in subjects with dry eye disease

Study Design:
Phase 3, multicenter, randomized, controlled, double-masked study of the safety and efficacy of sodium hyaluronate ophthalmic solution 0.18% vs vehicle in subjects with dry eye disease

Study Population:
The original sample size estimated the need for approximately 300 subjects (150 per group) at approximately 45-60 clinical sites in the United States (US). *As a result of the protocol defined interim analysis, the sample size has been adjusted to 440 subjects (220 per group) at 15 clinical sites in the US.*

Subjects meeting the following criteria will be **enrolled** in the study:

4. Male and female adults aged 18 years and over
5. Female subjects must be at least 1-year postmenopausal, surgically sterilized, or have been utilizing one of the following systemic methods of contraception for at least 3 months prior to Screening and 1 month following study completion: oral, transdermal, implantable, injectable, or vasectomized partner. All female subjects must have a negative urine pregnancy test at Screening and Day 14 except women who are at least 1-year postmenopausal or status post hysterectomy or bilateral oopherectomy.
6. Subjects should have at least a 3-month documented history of dry eye in both eyes diagnosed as dry eye syndrome (disease), keratoconjunctivitis sicca (KCS), or due to Sjögren syndrome (immune exocrinopathy).
7. Subjects must experience **in the same eye at Screening and Baseline**
    - At least 2 symptoms of dry eye (soreness, scratchiness, dryness, grittiness, and burning)
        - rated as ≥ 2 (often) on the symptom frequency scale
        - scored as ≥ 50 mm on Visual Analogue Scale (VAS).

- The following objective parameters of dry eye syndrome (disease):
  - corneal fluorescein staining total score of ≥ 3
  - lissamine green staining total score of ≥ 3.

8. Subjects must agree to discontinue all artificial tears from Screening through the duration of the treatment period (Screening to Day 14).
9. Subjects who have taken Restasis® are eligible for inclusion if they have not used Restasis® during the 4 weeks prior to Screening.

Subjects who meet any of the following criteria will be **excluded** from the study:

1. Pregnancy or lactation
2. Females of childbearing potential who are not using systemic contraception, are not postmenopausal (≥ 1 year), or are not surgically sterilized
3. Unwillingness to discontinue artificial tears from Screening through the duration of the treatment period (Screening to Day 14)
4. Use of Restasis® within the 4 weeks prior to Screening or through the duration of the study period (Day 21)
5. Unwillingness to maintain present dosing regimen for all current medications
6. Contact lens wear from 1 week before Screening until conclusion of study participation by the subject (Day 21)
7. Ocular surgery (of any type, including laser surgery) or ocular trauma within the 4 months prior to Screening
8. Abnormality of the nasolacrimal drainage apparatus
9. Punctal occlusion or diathermy within 3 months prior to Screening
10. Other diseases or characteristics judged by the investigator to be incompatible with the assessments needed in this study or with reliable instillation of the study medication
11. Any active inflammation of the eye not due to KCS (eg, iritis, scleritis, etc.)
12. Participation in any other clinical trial within 30 days prior to Screening
13. Prior participation in a previous clinical trial of Vismed®

Test Product, Dose, and Mode of Administration:
One or two drops of SH ophthalmic solution 0.18% or vehicle, as allocated, will be instilled in each eye at least 3 and up to 6 times daily.

Duration of Treatment:
14 days

Efficacy Assessments:
Lissamine green staining of the conjunctiva and cornea; fluorescein staining of the cornea; Schirmer I testing; rating of symptom frequency; global scoring of symptom intensity by VAS; composite index of symptom intensity and frequency; and rating of impact of dry eye symptoms on daily life (see Sections 5.2.2.1 and 5.2.2.2). See Schedule of Events for details.

Safety/Tolerability Assessments:
Slit lamp examination, best-corrected visual acuity (BCVA), intraocular pressure (IOP), dilated fundus examination, and collection of adverse events (AEs; see Section 6). See Schedule of Events for details.

Statistical Methods:
The primary objective efficacy measure will be change from baseline at Day 7 in lissamine green staining (summed cornea + nasal conjunctiva + temporal conjunctiva scores, each on a 0–4 scale; maximum score 12). The primary subjective efficacy endpoint will be the change from baseline at Day 7 in global symptom frequency as rated on a 0–3 scale.

The primary objective and primary subjective analysis will assess the significance of the difference between SH ophthalmic solution 0.18% and control (vehicle placebo) with respect to change from baseline at Day 7 using a Wilcoxon rank sum test. Since this study aims to demonstrate superiority of SH ophthalmic solution 0.18% over vehicle, a one-sided test will be used. Thus, an alpha level of 0.025 will be used when assessing significance of statistical tests in the analysis of these endpoints. A masked interim analysis, conducted when approximately 200 of the planned number of subjects (N = 300) reach the primary endpoint to assess the adequacy of the planned sample size, will be performed. *The interim analysis demonstrated that modification of the sample size was required; the final sample size was 440 subjects (220 per treatment group).*

Initial sample size estimates were chosen based on the values obtained for the Baudouin 2005 study, the first Phase 3 study of SH ophthalmic solution 0.18%. For an alpha level of 0.025 and 80% power, the results show that for a difference between means of 0.91 and standard deviations of 2.45 and 2.72 for the active and vehicle groups, respectively, the sample size for each group is 150 (128 subjects adjusted by 5% to compensate for the test inefficiency and inflated by 10% to account for dropouts). Thus, a sample size of 150 in each group (N = 300) would have approximately 80% power to detect a between-group difference of 0.91 using a Wilcoxon rank sum test at an alpha level of 0.025. *The revised sample size of 220 in each group (N = 440) would have 84.4% power to detect a between-group difference of 0.91 using a Wilcoxon rank sum test at an alpha level of 0.025.*

10.3.2.2 Subject Randomization and Study Assessments

Evaluations will be conducted at the study site at Screening, baseline, and 2 treatment phase visits, according to the Schedule of Events. Subjects will be screened between 7 and 5 days prior to baseline (Day -7 to Day -5) to allow for a minimum run-in period of 5 days prior to entry into the study. Subjects must discontinue contact lens wear 1 week before Screening. Subjects who meet eligibility requirements at Screening will be asked to discontinue all artificial tears and will be given a supply of vehicle eye drops with instructions to administer 1 to 2 drops at least 3 and up to 6 times daily during the 5 to 7-day run-in. Subjects will be asked not to use vehicle eye drops for at least 4 hours before baseline assessments and measurements, and not to wear contact lenses from 1 week prior to Screening through Day 21.

At the Day 0 visit (Baseline); subjects who continue to meet eligibility criteria will be randomized to active study drug or vehicle. Randomized subjects will be instructed to instill 1 to 2 drops of study medication in each eye at least 3 and up to 6 times daily for 14 days. An adequate supply of study medication will be dispensed at Baseline. At Days 7 and 14, subjects will return to the study site for evaluations. A post treatment follow-up evaluation

will be conducted by telephone at Day 21, unless the subject has presented with or reports an AE, in which case a visit will be scheduled to evaluate the AE.

10.3.2.3 Treatment

At Day 0, after all Baseline examinations have been performed and eligibility for the study is confirmed, in the presence of the study personnel, the subject will apply 1 to 2 drops of the allocated study medication into each eye and will blink several times to allow the solution to spread over the cornea. He/she will be instructed to administer the study medication at least 3 and up to 6 times per day for 14 days. The subject will be instructed to use the same monodose for both eyes.

10.3.2.4 Efficacy Assessments

10.3.2.4.1 Objective Efficacy Measures

Lissamine Green Staining of the Cornea and Conjunctiva

Lissamine green staining will be performed in both eyes using one drop of 1% lissamine green solution, with results observed in low to moderate intensity white light of the slit lamp between 1 and 4 minutes following instillation. The areas evaluated will be the cornea and the nasal and temporal conjunctiva. Each area will be graded as follows, according to the proportion of the area that is covered by staining:

0 = 0%
1 = 1%–15%
2 = 16%–30%
3 = 31%–45%
4 = >45%

The investigator will record the total score per eye (the maximum score is 12 [maximum of 4 for each of 3 areas]). Lissamine green staining will be performed at all study visits (see Schedule of Events).

Corneal Fluorescein Staining

Fluorescein staining of the corneal epithelium will be performed in both eyes. Dye will be placed in the eye using blotting paper impregnated with fluorescein dye moistened with a full single drop (must be at least 10 µL) of buffered saline solution (BSS). The subject will be asked to blink several times in order to disperse the dye uniformly. The cornea will be examined 3 minutes after instillation using the cobalt blue filter of the slit lamp and a Wratten #12 yellow filter to view the surface of the eye and identify abnormalities where staining appears.

Fluorescein staining should be conducted prior to lissamine green staining, and the tests should be separated by at least 15 minutes.

Staining will be graded on a 4-point scale for 3 characteristics:

1. Type
   - 0 = No staining
   - 1 = Micropunctate (2-5 areas)
   - 2 = Macropunctate (> 5 up to 15 areas of punctate staining or 1 area of coalesced staining)
   - 3 = Coalescent macropunctate (> 15 areas of punctate staining or 2 or more areas of coalesced staining or any area of epithielial or stromal diffusion of fluorescein
   - 4 = Patch (> 15 areas of punctate staining and 2 or more areas of coalesced staining and a frank corneal epithelial defect)

2. Extent/Surface Area
   - 0 = 0%
   - 1 = 1%–15%
   - 2 = 16%–30%
   - 3 = 31%–45%
   - 4 > 45%

3. Depth
   - 0 = No staining
   - 1 = Superficial epithelium
   - 2 = Deep epithelium, delayed stromal glow
   - 3 = Immediate localized stromal glow
   - 4 = Immediate diffuse stromal glow

The investigator will record the total score (type + extent + depth, maximum score is 12 per eye). Fluorescein staining will be performed at all study visits (see Schedule of Events).

Schirmer I Test

The Schirmer I test will be performed in both eyes without anesthesia and before any testing that requires topical anesthesia (applanation tonometry). The subject should be sitting comfortably in a room without extremely bright lighting. The filter paper strips will be placed at the junction of the middle and lateral 1/3 of the lower eyelid, avoiding contact with the cornea. Strips should be placed in both eyes at the same time and timed for 5 minutes. The subject may sit with their eyes gently closed during this period and should avoid excessive blinking during the test. Strips will be removed after 5 minutes and the amount of wetting is recorded in mm. The subject should be reminded not to rub his/her eyes for at least 30 minutes after the completion of the test. Schirmer I testing will be performed at Days 0, 7, and 14 (see Schedule of Events).

10.3.2.4.2 Subjective Efficacy Measures

Global Symptom Frequency

The frequency of symptoms will be assessed according to the following rating scale:

0 = Never
1 = Sometimes
2 = Often
3 = Constantly

The frequency rating is assigned by the subject for each of the dry eye symptoms based on global evaluation of the 2 eyes. The subject will grade each symptom: soreness, scratchiness, dryness, grittiness, and burning. Then the 5 scores will be recorded. Symptom frequency rating will take place at all study visits (see Schedule of Events).

Global Symptom Intensity

The 100 mm VAS will be used at each visit to assess the presence and severity of dry eye symptoms: soreness, scratchiness, dryness, grittiness, and burning (0 = no symptom and 100 = severe symptom). The subject marks the point on the scale that best depicts each symptom, and the distance between the 0 point and the subject's mark is measured in mm by the study staff and recorded. Symptom intensity rating will take place at all study visits (see Schedule of Events).

Composite Index of Global Symptom Intensity and Symptom Frequency

The composite index of global symptom intensity and symptoms frequency score will be calculated as follows:

$$\text{Composite index} = (\text{VAS x frequency})_{\text{soreness}} + (\text{VAS x frequency})_{\text{scratchiness}} + (\text{VAS x frequency})_{\text{dryness}} + (\text{VAS x frequency})_{\text{grittiness}} + (\text{VAS x frequency})_{\text{burning}}$$

This index will be calculated as a part of the statistical analysis of the study, and as such, is not a separate procedure to be administered during the study.

Global Impact of Dry Eye Disease on Daily Life

Rating of the impact of the dry eye disease on daily life (eg, screen work, television viewing, reading, and driving) will be performed at each visit as follows:

0 = Absent
1 = Minimal
2 = Moderate
3 = Severe

The rating is assigned by the subject based on the perception of the global impact of the dry eye symptoms on activities of daily living. After being asked to consider the impact of the

dry eye symptom on daily activities such as screen work, television viewing, reading, and driving, the subject will assign one overall score. Rating of the impact of symptoms on daily life will take place at Days 0, 7, and 14 (see Schedule of Events).

10.3.2.5 Safety Assessments

The following will be assessed at each visit on each eye:

Slit Lamp Examination

A routine slit lamp examination will be performed to evaluate the anterior segment of the eye, including lids, cornea, sclera, conjunctiva, lid margins, lens, and capsule. Abnormalities will be documented. A slit lamp examination will be conducted at all study visits (see Schedule of Events).

Best-Corrected Visual Acuity

BCVA will be measured through a pinhole, unaided, or using the subject's historical correction at a distance of 20 feet (6 meters) using a Snellen chart. The last complete line read by the subject will be documented without the use of "+" or "-" variables. Any decrease of 2 or more lines of visual acuity during study participation will be considered an AE and all appropriate documentation and reporting will be done. BCVA testing will be conducted at Screening, Days 0, 7, and 14 (see Schedule of Events).

Intraocular Pressure

All IOP measurements will be performed utilizing Goldmann applanation tonometry using either a combination anesthetic/staining agent (eg, Fluress) or a topical anesthetic (proparacaine, tetracaine, etc.) in combination with a separate staining agent (eg, fluorescein). All pressure will be recorded in mmHg. All IOP measurements are to be obtained and recorded for the right eye first and repeated for the left eye. IOP measurement will be conducted at Days 0, 7, and 14. IOP measurement will be the last ophthalmic procedure conducted at these visits except for Day 14 when it will immediately precede the dilated fundus examination.

Dilated Fundus Examination

On visits requiring a fundus exam, the pupils should be assessed for any abnormalities, then a dilating drop (or set of drops) instilled. The dilating drop(s) used routinely in the office in the physician's normal standard of care may be utilized. Once full dilation is achieved, the fundus exam will be performed to evaluate the health of the optic nerve, retina, and macula. The fundus examination will be conducted at Screening and Day 14, and will be the last ophthalmic procedure performed at these study visits.

Adverse Events Assessments

An AE is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding),

symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

Performing Adverse Events Assessments:

AEs will be assessed at each study visit, once subjects receive the first dose of study drug (Days 0, 7, and 14). To elicit AEs, simple questions with minimal connotations should be used as the initial questions at all evaluation points during the trial.

For example:

How do your eyes feel?
Have you had any health problems since your last assessment?

The AE probe should be conducted by the same study personnel for each visit for an individual subject, if at all possible.

All AEs, regardless of severity and whether or not they are ascribed to the study treatment, will be recorded using standard medical terminology. The onset, duration, severity, action taken, relationship to treatment, and outcome of all AEs will be documented in the Case Report Forms (CRFs) or electronic CRFs (eCRFs). The investigator must assess (and record in the CRF and in the source documents, or eCRF) the degree to which the event was related to the study medication. Subjects with an AE should be carefully followed to determine outcome until resolution or 30 days after the last study visit (Day 21), whichever comes first.

If no AE has occurred, this should be noted in the appropriate place on the AE section of the CRF.

Timing

Any AE that begins from Day 0 until Day 21 is to be recorded in the source documents and in the appropriate section of the CRF. All events reported from Screening until Day 0 will also be recorded as AEs. Subjects with an AE should be carefully followed to determine outcome until resolution or 30 days after the last study visit (Day 21), whichever comes first.

Severity

The investigator will use the following definitions to code the intensity of the event:

mild usually transient, requiring no special treatment, and does not interfere with the subject's daily activities

moderate traditionally introduces a low level of inconvenience or concern to the subject and may interfere with daily activities, but is usually relieved by simple therapeutic measures

severe causes an interruption of the subject's usual daily activity and traditionally requires systemic drug therapy or other treatment

There is a distinction between the severity and the seriousness of an AE. Severe is a measurement of intensity; thus, a severe reaction is not necessarily a serious AE (SAE). For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for SAEs (see Serious Adverse Events).

Relationship

The relationship or association of the study medication to an AE, as causing or contributing to the AE, will be characterized as defined below:

not related	evidence indicates no plausible direct relationship to the study medication
unlikely related	suggests other conditions are reasonably likely to account for the event including concurrent illness, progression, or expression of the disease state, or reaction to concurrent medication
possibly related	suggests that the association of the event with the study medication is unknown; however, the AE is not reasonably supported by other conditions
related	follows anticipated response to study medication and is confirmed by discontinuing and/or rechallenge

Procedures such as surgery should not be recorded as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of AE as described (see Adverse Events Assessments).

Expectedness

AEs in clinical trials considered by the investigator to be related to study drug have been uncommon (seen in only 1.4% of subjects in the largest trial to date). Those events that are expected are listed in the Investigator's Brochure (IB).

Unexpected AEs are defined as any AE, the specificity or severity of which is not consistent with the current IB.

Clinical Significance

The medical monitor, in consultation with the investigator, will be responsible for determining whether an AE is clinically significant for the subject or the study overall.

Serious Adverse Events

Definition

An SAE is defined by federal regulation as any AE occurring at any dose that results in any of the following outcomes: death, life-threatening, hospitalization or prolongation of existing

hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Reporting Serious Adverse Events

Investigators must phone and fax the completed SAE report form with all available information within 24 hours of learning of the SAE to the medical monitor.

All follow-up information to SAEs must be provided to the medical monitor within 3 calendar days of receipt at the site.

The investigator must notify the approving Institutional Review Board (IRB) of any SAEs regardless of cause within 24 hours.

The medical monitor will be responsible for reporting SAEs to the Food and Drug Administration (FDA).

The investigator must provide a written report of any SAE to the IRB and to the medical monitor. In this report, the investigator will advise whether or not the SAE is judged to be related to administration of the study drug. All subjects who experience an SAE should be followed clinically and undergo the appropriate diagnostic evaluations until stabilization or resolution of the event.

For any death occurring through the end of the study, regardless of the degree of relationship to study drug, the SAE resulting in the death must be reported to the medical monitor. This should take place regardless of how much time has elapsed since the last exposure to study drug. A death occurring after completion of the study that is not reasonably associated with study drug administration does not require the completion of an AE report.

10.3.2.6 Schedule of Events

Evaluation	Screening Days -7 to -5	Baseline Day 0	Day 7 ± 1	Day 14 ± 1	Telephone Safety Follow-up: Day 21 ± 3
Signed informed consent	X				
Inclusion/exclusion criteria	X	X			
Demographics	X				
Medical history	X	X[a]			
Ocular history	X	X[a]			
Symptom intensity grading with Visual Analogue Scale (VAS)	X	X	X	X	
Symptom frequency rating	X	X	X	X	
Rating of impact of dry eye on daily life		X	X	X	
Best-corrected visual acuity (BCVA)	X	X	X	X	
Corneal fluorescein staining[b]	X	X	X	X	
Lissamine green staining	X	X	X	X	
Slit lamp examination	X	X	X	X	
Schirmer I test		X	X	X	
Intraocular pressure[c] (IOP)		X	X	X	
Dilated fundus exam	X			X	
Urine pregnancy test[d]	X			X	
Randomization		X			
Drug administration		X			
Drug accountability		X	X	X	
Adverse event (AE) assessment		X	X	X	X
Prior/concomitant med assessment	X	X[1]	X	X	

a. Brief review

b. Fluorescein corneal staining should precede lissamine green staining. The procedures should be separated by at least 15 minutes.

c. IOP should be the last ophthalmic procedure to be performed **except for at Screening and Day 14** when it will directly precede the dilated fundus exam.

d. Only females of childbearing potential who are not postmenopausal (≥ 1 year), or are not surgically sterilized